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CORNELL CONFERENCES ON THERAPY

VOLUME SEVEN

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MOTTO

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No way of thinking or doing, however ancient,
can be trusted without proof

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HENRY DAVID THOREAU

Introduction to the Series

The art of treatment represents the merger of two independent bodies of knowledge In their development the two disciplines have followed separate lines at times so far apart that little relationship between them is discernible The science of pharmacology is often and properly concerned with impractical matters and a large part of therapeutic knowledge is of necessity an anthology of purely empirical experience

Forces appear to be at work which prevent their free interplay even though the fact has received universal recognition that the best interests of medical practice can be served only by their appropriate integration It is the rare medical curriculum in which pharmacology and therapeutics are so arranged as to have their teachings woven into a single design The courses of pharmacology are isolated in a term or two in advance of the bulk of therapeutics and to a considerable extent clinicians continue to build the structure of therapeutic teaching with indifferent regard for the pharmacologic base already set for its support

There is in fact in evidence a degree of competition and distrust between the two Students are informed that thus-and-so is true in the treatment of the patient in spite of what pharmacology offers to the contrary There is the implication that the one is practical the other theoretic and hence irrelevant This attitude toward the relationship between pharmacology and therapeutics is more apparent in some schools than in others but none is wholly free of it It is of course unsound for in any system of rational treatment the two are no more separable than the two faces of the same coin

In ward and clinic the student is often told to do what in pharmacology he has been taught to avoid, and, conversely, in pharmacology he often learns to expect what turns out to be alien to the experience of the clinic. It is quite clear that neither has taken full advantage of the opportunities afforded by the other. It is also clear that there is an urgent need for a forum where pharmacologists and clinicians may come together and talk these things over. That, in essence, is the purpose of the Conferences on Therapy.

The Cornell Conferences on Therapy were inaugurated in 1937 as a joint venture of the Departments of Medicine and of Pharmacology. Arrangements were made for the participation of every department of Cornell University Medical College—New York Hospital, and the collaboration of other institutions. They are scheduled throughout the larger part of the school year. It is the policy to begin on time and end promptly at the close of an hour.

There is considerable latitude in the conduct of the conferences. Certain features characterize the majority of them. A group of drugs, a therapeutic procedure, a symptom, or disease is selected as the topic for discussion. Practical procedures for the use of the therapeutic measures are outlined by a clinician, and, where feasible, a résumé of the experimental basis is presented by someone trained in the more basic sciences of physiology, pharmacology, or chemistry. Approximately half of this period is devoted to informal discussion in which the audience is encouraged to take an active part.

Free use has been made of the question as an especially effective device for exciting interest and focusing attention. In some conferences the method of the "round table" discussion is employed, the questions being directed to a group of experts on the subject. The most successful conferences are among those in which the largest part of the session is devoted to informal discussion through the medium of questions and answers. Those, in which sharp differences of views develop and the evidence is probed, acquire a particularly stirring and stimulating quality. Therapeutic prejudice and

vague opinion have a somewhat difficult time of it in these conferences

The scope covers the whole range of therapeutics To qualify for a conference, a subject must be a problem of therapy It may be old or new It should be important If there are widely divergent views concerning it, so much the better, since it is the function of the conference to point out how the evidence stands The order of subjects doesn't matter A series of conferences in a particular field has been attempted from time to time, as one series on the treatment of the blood diseases On the whole, it has seemed more practical to avoid the series on any one subject, and to take up such topics as seem feasible in relation to their interest at the time and the personnel available to lead the discussion

While the introductory remarks are often prepared, the discussion is for the most part unrehearsed and extemporaneous In many cases the chairman tries to lead the discussion into a planned direction, but frequently the course is determined by the nature of the questions in which the audience appears to show the greatest interest

The conference is no substitute for the formal lecture, the scientific article, or the textbook It is not a substitute for any traditional form of medical teaching It does not aim to treat any subject exhaustively, but only to explore some aspects of special interest to analyze the evidence on controversial points of opinion and practice, to elaborate the physiologic, pharmacologic, and chemical bases of therapeutic measures and to present these on the level of the general practitioner

There has been a good deal of experimentation in policy and technics Certain features have survived The purpose—to stimulate interest in rational therapy, the method—spontaneous informal and free discussion

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a permament record would enhance their value. Accordingly, they were taken down by a stenotypist in attendance at each session. The success of the edited record led to the next step, the introduction of the conference to a wider audience through their monthly publication in the *Journal of the American Medical Association* from 1937 to 1940. In 1940 this system was transferred to the *New York State Journal of Medicine.* A new monthly publication whose policy is to make more accessible to the general practitioner the specialized fields of clinical science, the *American Journal of Medicine,* expressed an interest in printing the edited record of some of these conferences. Accordingly, the monthly publication system was revised, and since 1946 the plan was adopted to print conferences in both the *New York State Journal of Medicine* and the *American Journal of Medicine.*

Through their publication it was hoped that they might serve to demonstrate some of the advantages of this method of learning and lead to its adoption by other institutions. It is a method which can be readily adapted to the needs and means of small medical communities and hospital groups.

There has been widespread interest in the publication of these conferences. From the large volume of correspondence and the nature of the comments, it has become clear that they are filling a need in medical education. Busy physicians find them a rich source of authoritative information in therapeutics, made more practical by the exchange of views among specialists and general practitioners, made more accessible by the restriction of their scope and the easy stirring style of the conference method.

In response to numerous requests, the final step in their evolution was taken, namely, the annual publication of a volume representing a group of conferences selected in the main for their quality and enduring value.

THE EDITORS

Preface to Volume VII

The select group of fifteen conferences included in this volume covers a wide scope of subjects in therapeutics general and specific. At the beginning in the listing is the provocative discussion of the question of how to evaluate any drug clinically and at the end a conference on such a specialized topic as the surgical management of mitral stenosis Every endeavor has been made to include important current developments in the general field of treatment but presented in such a fashion as to keep before the reader their relation to broad principles and experiences of the past In the editing of the stenotype notes special attention was paid to the problem of reproducing in the printed record as much as possible of the spirit of the informal discussion and free inquiry that animated those who participated It should add much to the ease and interest of reading

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List of Conferences

References to conferences in Volume VII (1) *Am J Med*, 17 722 (Nov) 1954 (2) *Am J Med* 17 271 (Aug) 1954 (3) *New York State J Med* 54 2953 (Oct. 15) 1954 (4) *Am J Med* 16 118 (Jan) 1954 (6) *Am J Med*, 17 395 (Sept) 1954 (13) *New York State J Med* 54 2343 (Aug) 1954 (15) *Am J Med* 18 326 (Feb) 1955

Dr. William J. Grace: It is well known that the response to a particular pharmacologic agent in a group of patients is not invariably the same or even predictable. When we learn that a certain agent proved effective in, say 35 per cent of the patients, we accept the result and let it go at that. This is one way of evaluating a therapeutic agent; but there are other questions which need to be raised and answered, and I will confine my comments to some of the experiments that we have recently made in this connection. I refer to the matter of determining the factors in any particular individual which alter the responses to the drug in question from time to time. It helps to understand why an agent may fail to work at one time or produce more effect than anticipated at another.

We have had an opportunity to make a variety of observations on the responses of the gastrointestinal tract during various mood and feeling states in our subject, Tom, a man with a gastric fistula. In one instance, he was lying on the table and carrying on a free discussion of appetizing foods which appealed to him. This was late in the morning; he felt hungry and expressed a desire to eat. At this time the stomach showed an increase in blood flow, total acid secretion, and gastric motility. Under these circumstances the introduction of beef bouillon into the stomach was followed by further increase in blood flow and secretory and motor activity. The result was different when the same experiment was made at a time when the subject felt discouraged and depressed, preoccupied with self-criticism because of his inability to effectuate a deal in the purchase of a house. During this period he complained of fullness after eating, lack of appetite, and loss of interest in eating. At this time the same beef bouillon stimulus was followed by little or no change in the secretion or motor activity of the stomach.

Changes in stomach function during anger were observed in this subject. Tom was discussing his attitude towards a man who had recently discharged him from his employment under circumstances which the subject felt were [illegible] and humiliating. He showed [illegible] In th[illegible] stomach showed an increase i[illegible], hydro[illegible] and motility.

During fear the opposite was noted. Tom was suddenly faced with the fact that his supervisor would soon become aware of Tom's lack of attention to carrying out the jobs that he had been assigned. The professor entered the laboratory and searched for a protocol book which Tom was supposed to have filed. Tom became frightened that his laxity would be discovered and he would be discharged. However, the professor found the book and walked out satisfied. Sharp changes in the behavior of the stomach took place. During the sudden experience of great fear there was blanching of the mucosa, decline of secretion, and cessation of motor activity. During the period of recovery of confidence, the blood flow increased, and motor activity rapidly returned. Such changes in either direction occur rapidly without the individual necessarily verbalizing any feeling state that may be associated with them. In the laboratory, changes often appeared in the stomach before the particular drug was introduced. The nature of the change depended on his attitude at the time. For example, when Tom was frightened by the prospect of taking a large and disagreeable-looking pill, his stomach became pale and hypoactive before the medicament was administered. On another occasion Tom became angry at being given an injection. Hyperfunction of the stomach was noted before the injection.

When the subject ate an average meal at a time when he felt hungry and interested in eating, the gastrocolic reflex was brisk, resulting in increased blood flow, motor activity, and secretory activity in the large bowel. It was not brisk, however, when the food was introduced directly into the patient's stomach or when he forced himself to eat without much appetite. Under these circumstances none of the changes indicating activity of the gastrocolic reflex took place.

An attempt has been made to get around the difficulty of persons reacting differently to different laboratory situations by making use of a standard type of stress stimulus. This has not proved very successful, since different persons exposed to the same trying circumstances react in different ways. In one group of experiments observations on the large bowel were made while the subjects were exposed to the stressful

use of a placebo is considered by many physicians objectionable in a method of clinical evaluation and why there seems to be so much resistance to the idea that the experimenting doctor and the patient should remain in the dark about the identity of the agent until the comparison is finished.

Dr. Frank C. Ferguson, Jr.: Dr. Grace has cited examples showing how the patient's moods can influence the effects of a drug. Could we hear something about the influence of the doctor's attitude on the effects of a drug?

Dr. Gold: It is not difficult to find examples of the profound influence of the doctor's attitude. The case of khellin is a good illustration of recent vintage. This material was introduced a few years ago for the treatment of cardiac pain in coronary disease and of bronchial asthma on the basis of laboratory experimentation showing that it exerts a potent smooth-muscle relaxing action. Clinical trials proved that by far the larger proportion of patients with angina pectoris obtained partial or complete relief from this drug. A placebo was used in some of these studies, but the physician knew which was which at the time of his questioning the patients. A group of us undertook the investigation of khellin by the double-blind test, using a placebo which in physical appearance was indistinguishable from the tablets of khellin, and arranged observations in such a way that neither the patient nor the doctor was aware of the identity of the two materials until the results were all in and analyzed. After some 3000 answers regarding the effect on pain of the placebo and khellin given to the same group of patients, the results showed that if the patient and the doctor were kept in the dark regarding the identity of the agents, the placebo and khellin could not be distinguished with respect to the effect on cardiac pain.

It runs through the whole history of therapeutics, especially that having to do with the action of drugs on subjective symptoms, that the verdict of one study is frequently reversed by another unless one takes measures to rule out the psychic effect of a medication on the patient and the unconscious bias of the doctor. The double-blind test insures this.

Dr. Ferguson: You speak of the need for the double-blind

test in cases where drugs are tested for their effects on subjective symptoms, how about so-called objective matters? Do you believe that the double blind test is necessary there to avoid error in interpretation?

Dr Gold I think it is well that you used the term "so-called objective" I am beginning to wonder whether there are any truly objective observations In the study of drugs in hypertension, a measurement of the blood pressure would certainly seem to be an objective criterion, but I have a notion that the reading of the blood pressure also depends on how the doctor feels about the agent Subconscious bias is a very subtle mechanism Results of a study gain considerably in validity if the doctor making the observation, subjective or objective in nature, does not know whether it is the placebo or the medication in question he is concerned about

Dr Benjamin Jablons How important would a placebo be in evaluating a diuretic agent, since the reaction there involves the electrolyte balance?

Dr Gold I suppose by evaluation of a diuretic agent you mean determining its potency

Dr Jablons Yes

Dr Gold In that case, of course, the particular agent is compared with a standard What would you think, Dr. Cattell, about the need for a double blind test in a comparison involving a diuretic effect as a measure?

Dr McKeen Cattell It should be done as a double blind test. There is always the possibility of a subjective element coming into the experiment at one point or another and influencing the results

Dr Paul Reznikoff One of the least subjective measurements is that of the iron content of the blood in an anemic patient in following the improvement in the hemoglobin value during medication Attempts are made to diminish dependence on subjective impressions and verify results with hemoglobin values and hematocrit readings In these patients attempts have been made to determine the relative value of various iron compounds and on the basis of such objective measurements it has been stated that some forms of iron are

Dr Irwin D J Bross I am very much impressed with the remarks I heard today It seems as though this group has a level of sophistication that I have not often encountered in my work with medical groups I might say a word about this third person who was mentioned by Dr Quick I guess this is more in the nature of a statistician's type of third person He can be replaced by a machine The reason I mention this is that frequently it is convenient to have the decisions made by a third person There are many situations in which de cisions can be made by a pair of dice which represent a third person in this particular sense If a pair of dice sounds un scientific, you can call it randomization, and you can use a random number table which is perhaps not as illegal looking as a pair of dice

Dr Ferguson Since the matter of statistics has been brought up, I should like to remark that I have an intense prejudice against the mass of statistics that accompanies the introduction of new drugs It seems to me that statistics as they are so often used are too often misleading Many people believe that they eliminate chance, when in fact they merely give an idea as to the probability of the results being due to chance There is also the fact, which is often overlooked, that statistical analysis of the results does not correct the defect of a bad experiment

Dr Bross Yes, but I want to point out where statistics do come in Actually, there are two things which interfere with the evaluation of drugs The first is what might be termed the experimental error, sampling variation This is essentially the factor that is supposed to be controlled by statistics The second thing is the particular factor that has received especial attention today, namely, bias The standard statistical tests do not themselves control bias Analysis by statistical technics is based on the assumption that the results are unbiased I would agree, therefore, that there is a great deal of statistical, or presumably statistical material which is published that is completely misleading simply because of the belief that all that is necessary to solve a problem is to put down a little statistical arithmetic Much more than that is necessary The problem is much more complicated

Dr. Gold: I presume that the item to which you refer is the design as to bias before the experiment is actually carried out.

Dr. Bross: Yes, the design as to bias.

SUMMARY

Dr. Gold: This conference directed its attention to the problem of the clinical evaluation of new medicinal agents as one of the major issues in therapeutic progress. In the comparison of one drug with another the question of how to secure verdicts which stand a reasonable chance of escaping reversal was elaborated in the discussions this afternoon. In an account of interesting experiments on the gastrointestinal tract it was pointed out that the effect of a drug varies greatly with the patient's mood and that the effect may be significantly altered with a change in the mood. The discussion indicated how such factors might change results in the evaluation of a therapeutic agent. Special attention was directed to the use of the placebo, the double blind test, statistical analysis of the data, and experimental design to eliminate bias Emphasis was placed upon the unconscious aspects of bias of the physician, a subtle mechanism which in defiance of his best intentions may give rise to misleading results It was a noteworthy feature of the various discussions that the control of this factor by the double-blind test is now recognized as imperative for the valid evaluation of medicinal agents, not only with respect to the study of subjective symptoms such as cardiac pain, but in studies involving so-called objective measurements such as iron in anemia, diuretic agents, and anticoagulants in thrombotic diseases The conventional design of the treated and untreated groups in a clinical evaluation of a medicinal agent is giving way to the plan which calls for treating all patients where possible with the agent in question or a placebo, the two being indistinguishable in physical form or appearance and their identity unknown to patient or investigator during the experiment.

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are so many preparations and mixtures of digitalis substances. I was interested in noting a statement of William Withering in his discussion of foxglove in 1785 that "the more we multiply the forms of any medicine the longer we shall be in ascertaining its real dose." The basic dictum in regard to dosage has been stated many times before, but it can bear repetition. One should give that amount of the preparation which produces the optimum benefit one is seeking without producing toxic effects. There is need for two types of digitalis preparations, one to meet the needs of the majority of patients in the treatment of congestive failure and the other for the relatively small percentage of patients who require emergency care.

We have been using digitoxin as the drug of choice in the treatment of non-emergency congestive failure. It is a fairly constant preparation and not subject to the objections inherent in the bio-assay of the crude preparations and mixtures. Its actions are practically identical with those of digitalis leaf preparations both in speed of onset and the duration of action. We prefer this preparation also because of the fact that in situations which require rapid treatment, although not so urgent as to need an extremely rapid onset of action, one can give a large dose of digitoxin at the beginning without causing nausea and vomiting. We are guided in our observations in any particular patient by the fact that an oral dose of digitoxin produces considerable effect in about an hour, more quickly—within 10 to 20 minutes—with an intravenous dose, that the peak action is reached in the range of from 6 to 8 hours, and that during the next 2 or 3 weeks the effect gradually wears off. It is best given by mouth. There are occasional instances in which the intravenous route is necessary. There is a preparation of digitoxin in 40 per cent alcohol which may be given by intravenous injection but should be diluted 4 times before injection to reduce the alcoholic content to 10 per cent. Nearly all the patients that we see can be managed satisfactorily with digitoxin. The range of doses required for adequate initial digitalization is between 1 and 1.8 mg. Very few patients

require doses outside this range and many patients as has been well shown by Dr Gold can be digitalized adequately with 1 2 mg of digitoxin Many patients however especially advanced hospital cases require as much as 1 4 to 1 6 mg We usually start with 0 8 mg I have never seen toxicity from this dose It is followed by 0 4 mg in 6 hours The interval of 6 hours is used because it takes as long as that to produce the full effect of the previous dose and the result is used as a guide for adjusting the next dose The ventricular rate in the patient with auricular fibrillation serves as a good guide to adjustments in the dose The problem is more difficult in the case of the normal sinus rhythm In these we also usually give a total of 1 4 occasionally 1 6 mg at most 1 8 mg This takes about 18 hours The maintenance requirement of digitoxin has been fairly well established It lies somewhere between 0 1 and 0 2 mg a day Very few patients require less than 0 1 and very few more than 0 2 A daily maintenance dose of 0 15 mg has become fairly popular, and one of the firms has now prepared a tablet of this size

As far as we can observe the toxic manifestations of overdosage of digitoxin are identical with those of digitalis Loss of appetite is the first effect It is soon followed by nausea and then by vomiting Ventricular premature contractions and prolongation of the P R interval in the electrocardiogram also occur It has been said that digitoxin is particularly prone to produce toxic rhythms but this has not appeared in our experience

The kind of patients whom we encounter at Bellevue Hospital make it necessary for us to have on hand a preparation of the digitalis group more suitable for the acute emergency I refer particularly to the case of acute pulmonary edema often with very rapid auricular fibrillation Ouabain has here been the drug of choice for this purpose during the past 30 years perhaps longer Most people seem to think of this as a very toxic drug I believe this reaction is the result of some traditional misconception We find it perfectly safe The intravenous injection produces effects within a few minutes and the maximum action of a dose develops

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or very slow ventricular rate in auricular fibrillation, or premature contractions, or nausea and vomiting, it is well to assume that the patient has had as much digitalis as is advisable, or has even had an overdose, and that even full digitalization was not sufficient to prevent the attack of pulmonary edema Nothing is to be gained by giving more of a digitalis material, not to speak of the danger of doing so On the other hand, if there are no toxic effects, if there is a rapid heart rate with auricular fibrillation, or a rapid sinus rhythm, it would be wise to assume that the patient has not had enough of the previous digitalis material and to proceed to use ouabain intravenously in the endeavor to clear the pulmonary edema In such a case, the dose which Dr Luckey mentioned, 0 25 mg, may be safely given at one time Such a dose will not produce serious toxic effects in a patient who shows no toxic effects, irrespective of the amount of a digitalis material he has had before This dose may then be repeated at intervals of an hour in the manner in which Dr Luckey mentioned, being guided by the evidence of action I think it is a safe assumption to make that if the patient shows no toxic effects an hour after an intravenous dose of 0 25 mg ouabain, the repetition of this dose would at the most cause only very minor toxic effects Such increments of dosage given in this way are perfectly safe

Dr John S LaDue I might supplement these remarks by an observation we made some time ago in a group of 104 patients with congestive failure They were all receiving full maintenance doses of digitalis We then gave them lanatoside C intravenously in amounts up to full digitalizing doses, 1 6 mg In this group, 6 7 per cent developed toxic reactions, an incidence of toxicity for this dosage of lanatoside C previously found for patients who were not under the effects of digitalis I would not recommend this as a practice, but it serves to emphasize the safety of this intensive form of digitalization

One more point It has been our impression that patients in frank congestive failure require two to three times as much digitalis to keep the condition in order as those in whom

results in a group of patients with auricular fibrillation and failure of moderate severity in connection with a comparison of ouabain with acetyl strophanthidin. There we found that the single dose of 0.5 mg. ouabain or 5 cat units intravenously produced the same kind of effects we had previously observed in connection with single doses of 3 or 4 cat units of digitoxin. These are more nearly comparable kinds of experiments and in these the doses of the two compounds in terms of cat units come more closely together.

Dr. Luckey: In our observations at Bellevue, we found that 0.5 mg. of ouabain was inadequate in patients with auricular fibrillation. At the end of an hour the heart rate was still in these cases well above 100 a minute.

Dr. Gold: An hour is not always long enough for the full effect. But as I have already indicated, I agree that 0.5 mg. or 5 cat units is not sufficient in the advanced cases of failure. They require more ouabain as they require more of any other digitalis material.

Dr. Modell: I am inclined to agree with Dr. Gold that an assumed difference between the cat and man does not explain the difference in ouabain and digitoxin dosage.

Dr. Gold: In order to complete the story, it would be well to mention that there are very great differences between different digitalis materials in the dosage required in terms of cat units, but only when these materials are given by the oral route. It is to be remembered that the bio-assay method calls for a comparison of two materials by the intravenous route in animals. This comparison tells nothing about one of the most important properties of digitalis materials, differences in their absorption. And so it is that two materials may have the same potency by the intravenous route, the same potency in terms of cat units or U.S.P. units, but it may take many times as much of one as of the other to produce therapeutic effects when the two are compared by the oral route. This is one of the weak spots in the intravenous method of bio-assay, its failure to reveal differences in absorption which are so important when the drugs are used by mouth.

Dr. Luckey: The point which you made regarding the

difference between the single dose and the series of divided doses is in line with the observation by Cohen and Levy some years ago They did not happen to give 1 mg of ouabain intravenously at one time, but 0 5 mg, repeated in an hour, and in this form of dosage, they observed a considerable amount of toxicity, short runs of ventricular tachycardia in about 50 per cent of their patients

Dr Gold That is exactly what I would think would happen If the fractions are too close together, the total dose of 1 mg of ouabain will cause a good deal of toxicity If the fractions are smaller and the intervals longer, as should be the practice in the interest of safety, it is found that many patients will require as much as 1 mg total to induce the full effects

Dr Modell I wonder if we might not draw the conclusion from this discussion that the caution which has been suggested of dividing the 3 or 4 cat unit dose of digitoxin into fractions given at intervals is really not necessary, since it seems to be safe to give as much as 5 cat units of a digitalis material like ouabain at one time by the intravenous route without toxicity

Dr Gold Dr Luckey, perhaps you will try your hand at that question Why do you recommend splitting up the digitalizing dose of digitoxin and giving only 0 8 mg at the start?

Dr Luckey I think that in that way we protect the 2 or 3 per cent of the patients who vomit from the single dose of 1 2 mg I believe that it is a mistake to think of digitalis intoxication as merely a matter of nausea and vomiting During poisoning something more basic is also going on which is associated with a decreased efficiency of the myocardium Would you care to comment on that?

Dr Gold I am not quite sure what that means I was not aware that anything of consequence happens when the dose of a digitalis material oversteps the bounds a little bit and causes nausea or vomiting It is very disturbing indeed when the overdosage is extreme Your point is well taken, however, and I agree that it is well to guard against making

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people sick with digitalis if you can avoid it I would question whether you can avoid it completely I am inclined to doubt that starting digitoxin therapy with 0 8 mg and following it with 0 4 mg in 6 hours materially reduces the incidence of toxicity It lengthens out somewhat the course of digitalization, but in the case of a material like digitoxin which develops its action rather slowly, I would venture the guess that you end up with about the same incidence of nausea or vomiting I have been very much struck by the reports in the literature which rejected my suggestion for the use of 1 2 mg at one time in initial digitalization and then presented accounts of cases of toxicity in which that amount was given *in divided doses I think it is important for us* to fix in mind the fact that the most effective digitalis therapy is impossible without some incidence of toxicity There is involved here a basic law relating to variability in individual responses If you insist on a method of dosage which yields no minor toxicity, you sacrifice therapeutic efficiency One might put it in this way the best dosage of a drug is one which yields the highest incidence of therapeutic results not without toxicity but with a reasonably low incidence of minor toxicity I doubt that any good method of digitalization has ever been devised which in its application to large groups of patients will show less than about 1 or 2 per cent of minor toxic reactions

Dr Janet Travell I would like to ask Dr Gold to say something about some of the other preparations of digitalis besides the two that have been mentioned here, digitoxin and ouabain Are any of the others worth mentioning?

Dr Seymour H Rinzler I would like to extend that question Dr DeGraff and his collaborators have said a good deal about advantages in the matter of rapid excretion and greater margin of safety between the therapeutic and toxic dose for some of the other preparations How real are these things?

Dr Gold Perhaps Dr LaDue would like to comment on these points

Dr LaDue I believe there is a difference between digitalis

preparations in regard to the range between the therapeutic and toxic dose This range is smaller with some and larger with others We were led to this possibility by the experiments of Visscher at the University of Minnesota in which he showed with the heart lung preparation that there were very marked differences in the range between therapeutic and toxic doses for different members of the lanatoside series We then looked into this matter in the treatment of patients and we found that lanatoside C produced much less toxicity than ouabain or digitoxin in what seemed to be comparable doses in terms of cat units

Dr Gold In answer to Dr Travell s question concerning other materials of the digitalis group I might say a few words about Cedilanid or lanatoside C and digoxin These two materials have a shorter duration of action than digitoxin In some patients it is possible to repeat a nearly full digitalizing dose every second or third day without cumulative effects Much has been made of this fact as a supposed advantage over digitoxin the action of which lasts longer and attention has been focused in this connection entirely on the problem of overdigitalization It is probably an advantage in the most careless kind of overdigitalization The other side of this picture has not received the attention it deserves namely how uniform is the course of digitalis maintenance with preparations that are very rapidly excreted A lapse of 2 or 3 days in the dosage of digitoxin would not seriously upset the level of maintenance while in many cases such a lapse with Cedilanid or digoxin calls for redigitalization In the very unstable case of auricular fibrillation the rapidly eliminated materials like Cedilanid and digoxin sometimes present some difficulty in maintaining a smooth course Whether one considers the rapid excretion as an advantage or a disadvantage therefore depends on the point of view I am inclined to regard it as a disadvantage on the whole A kind of scare has been thrown into the subject of digitoxin therapy in statements regarding an alleged inordinately long duration of poisoning The fact remains that the patient who develops nausea or vomiting with digitoxin

recovers from it in a day or so in the vast majority of instances. This is indistinguishable from the picture of overdigitalization that we are all familiar with in the case of digitalis leaf which is still in many quarters a favored preparation.

I see that Dr. LaDue believes Cedilanid has a wider margin of safety than ouabain or digitoxin. I might call attention to the fact that in a recent report Batterman and DeGraff presented some figures showing that the margin of safety is essentially the same for Cedilanid, digoxin, digitoxin, and digitalis, but about 40 per cent greater in the case of amorphous gitalin which they now advocate as the preparation of choice. I presume, Dr. Rinzler, that your question has this report in mind. I recently had an opportunity to discuss this very matter as a member of a panel at the meeting of the American College of Physicians in Atlantic City. I don't believe they have established their point. Their data show differences in dosage as high as 700 per cent between the most susceptible and the most tolerant patients. I strongly suspect that a difference of 40 per cent in averages based on such a wide range of dosage would turn out to be a chance occurrence if the figures were subjected to statistical analysis. The notion of a greater "margin of safety" has great appeal, since every doctor would prefer to use the safer preparation, the one with the larger margin of safety. There have been many attempts to establish differences in the margin of safety for preparations of digitalis, but none has proved successful. The work of Visscher which was mentioned by Dr. LaDue showing differences in the margin of safety in heart-lung preparations of the dog has not been confirmed. Dr. Cattell and I showed that the same question receives different answers depending on the method used for ascertaining the margin of safety. There are many technical difficulties in the way of establishing differences in the margin of safety, and an entirely satisfactory technic for this purpose has never been devised. Beware of any claim for greater margin of safety. The method is full of pitfalls. The most prominent obstacle to a reliable comparison of margins of safety in man is the

technical difficulty of establishing with precision the minimal therapeutic and minimal toxic dose because of the numerous factors which can throw off both of these values in an actual determination

Dr Frank C Ferguson, Jr What do you use routinely for rapid digitalization?

Dr LaDue I give 1 6 mg of lanatoside C intravenously at one time taking 3 to 5 minutes for the injection This method is especially useful in the attempt to terminate a paroxysm of auricular tachycardia We have found it more successful than the method by which the dose is divided and fractions given at intervals of 2 hours Transient nausea and vomiting occur in about 8 per cent of the patients when the drug is given in this way but we have seen no serious toxicity

Dr Luckey I have heard others refer to this statement of Dr LaDue to the effect that the margin of safety is greater for lanatoside C than for other materials I am not impressed with the evidence In the studies with the heart lung preparations an expression of margin of safety was obtained by relating the therapeutic effect in the heart lung preparation with the dose required to kill the intact animal I would question whether such a ratio would have much meaning in the application to man

Dr Gold I agree with Dr Luckey There is no satisfactory evidence for the position that the margin of safety is materially different for the various members of the digitalis group If there is any difference I suspect it is much too small to reveal itself in the clinical use of the drugs

Dr Reader I have two questions Do you use the electrocardiogram routinely for the control of digitalization? Is it not true that a patient on a maintenance dose of digitoxin may go on for months without trouble and then develop minor toxic effects?

Dr Luckey In regard to your point about digitoxin toxic effects will of course appear if the maintenance dose is somewhat too large and exceeds in the particular individual the rate of excretion but this applies to digitalis as well

about 15 minutes for this compound. Have you had occasion to use it, Dr. Luckey?

Dr. Luckey: We have had very little experience with it. I think there has been a recent report to the effect that it is unduly difficult to control dosage. Is that incorrect?

Dr. Gold: I think you refer to a recent report in which a good deal of toxicity of acetyl-strophanthidin was shown; but if you will examine it, you will see that the doses were simply too large. That is the sort of thing that has given ouabain such a bad reputation for toxicity, excessive dosage. Dr. Modell, you might say a word about the dosage of acetyl-strophanthidin.

Dr. Modell: Acetyl-strophanthidin is one-half as potent as ouabain, and we found that 1 mg. produced the same effect as 0.5 mg. of ouabain. If one gives 0.5 mg. intravenously as the first dose and 0.25 mg. every 10 minutes until the desired concentration is built up to produce the effect one is after, one should encounter very little toxicity.

Dr. Gold: Our time is about up. I had the thought that a conference on the choice of a digitalis preparation would be marked by sharper controversy than has appeared in this conference. The literature gives one every reason for suspecting that opinions differ widely. You might be interested in knowing the estimate that more than one-half of all prescriptions written for any digitalis material in the United States today call for digitoxin.

SUMMARY

Dr. Gold: The perennial problem of the choice of a digitalis preparation and its most effective use was explored in the conference today in relation to current preparations and diversified experience. Digitoxin, digoxin, Cedilanid, ouabain, gitalin, acetyl-strophanthidin received attention from the standpoint of particular indications, dosage, and method of administration. Is a slowly or a rapidly eliminated digitalis material preferable for routine digitalization? Is there any advantage in dividing the 1.2 mg. dose of digitoxin into frac-

tions? Is there any difference in the margin of safety among members of the digitalis group? Do patients in advanced congestive failure require larger doses than those in mild failure? What is the meaning of the reported experience that a large dose of Cedilanid may be given to a digitalized patient without toxicity? Does it require more units of any one digitalis material than of any other to produce similar effects by intravenous injection? These are some of the propositions involving much debated questions which were subjected to analysis criticized, or defended in this conference Times have changed Digitalis leaf and the tincture were not even men tioned here When we were medical students and for some years thereafter the crude leaf and its galenicals were the preparations of choice There seemed to be no doubt from the discussion that for most purposes digitoxin has taken their place

fact that such very large quantities are necessary to produce results are responsible for the loss of interest in the ion exchange resins. They are not used nearly as much as they were a year or two ago.

The newest addition to the list of diuretics is the carbonic anhydrase inhibitor, Diamox (acetazoleamide) (It is now available for oral and intravenous use.) There is no question of the fact that it induces a very prompt diuresis when given intravenously and when given by mouth within a matter of 2 hours with a dose of 0.5 Gm. In the limited experience that has been reported thus far, this dose has produced no serious toxic effects when taken regularly for periods of about 6 months. The mechanism of Diamox diuresis is different from that of the mercurials. The mercurials lead to an increased excretion of sodium chloride with a concomitant loss of water. In the case of Diamox, there is an increase in the amount of bicarbonate excreted in the urine. There is very little if any increased excretion of chloride. There is also an increased excretion of potassium, in consequence of which there is more chance of hypokalemia in this form of diuresis than in the case of the mercurials. How troublesome this factor may be in relation to toxic effects is not yet established. It is easy to compensate for potassium loss by introducing it into the diet. There is the advantage in Diamox that it is effective by oral administration and thus far there seem to be few or no gastrointestinal disturbances. Time will tell what real limitations, if any, exist in the case of this drug, and whether it will prove in the long run substantially better than other agents that are now available.

Dr Reader: Thank you, Dr Modell. Perhaps this would be a good place to stop and see if there are any questions from the audience.

Dr Seymour H Rinzler: Would Dr Modell list the available oral mercurial diuretics?

Dr Modell: The latest member of the group is a material known as Neohydrin. There is a tablet of Mercuhydrin in combination with ascorbic acid, and there have been tablets of Mercuzanthin and of Salyrgan theophylline. It is my im-

pression that Neohydrin is the most popular at the present time

Dr Reader I wonder if Dr Gold would make some comments on this subject at this point?

Dr Harry Gold I should like first to shift the points of emphasis regarding the utility of different diuretic agents In the conventional way of telling the story of diuretics it is quite natural and I suppose quite appropriate to list most of the things that are being prescribed Dr Modell has followed that plan and has mentioned water xanthines ammonium chloride and urea I remember a recent talk on the subject in Atlantic City where someone mentioned a cup of coffee as a good diuretic It probably is quite effective a diuretic from the standpoint of disturbing the normal person s sleep but I am quite sure that few if any patients with cardiac failure and difficulty in breathing at night will find it much easier to breathe as the result of coffee That is what I think can be said about most of the oral diuretics at the present time It seems to me that at the moment the injectable organic mercurials occupy the stage almost by themselves In the curve of efficiency the drop from the injectable mercurial diuretics to the oral materials is precipitous and without the injectable mercurial diuretics I think that most of this great advance in the treatment of congestive failure in recent years would vanish What do you think about that Dr Luckey?

Dr E Hugh Luckey I agree

Dr Gold Most of the oral materials can in one type of experiment or another be shown to possess considerable diuretic action In an acute animal experiment ammonium chloride can boost the urine flow several hundred per cent However in an assay with ambulant patients in congestive failure the facts appear in another light A daily dose of 6 to 8 Gm of ammonium chloride causes a diuretic effect which is equivalent to approximately that of 0 5 to 0 75 cc of Mercuhydrin by intramuscular injection That is a fair effect but in order to get even that we used a dose which caused in about half of the patients gastrointestinal disturbances

sufficient to require the interruption of the drug. This is the way the thing looks in relation to most of the oral diuretics. There are under investigation nonmercurial oral diuretics of the aminouracil group. They also produce moderately effective diuresis, but only in doses which cause a fairly high incidence of gastrointestinal discomforts.

I should like to say a word about Neohydrin. It is an oral organic mercurial, immeasurably superior in its diuretic effects to the previous oral organic mercurials. It is possible to obtain with it diuretic responses equivalent to 1 cc. of injectable Mercuhydrin and sometimes more. The doses that are required may be fairly high, from 3 to 6 tablets a day or more. The indications are that gastrointestinal disturbances will ultimately make it impossible to continue the drug in many cases where the larger doses are necessary. However, it offers a distinct advance in diuresis by the oral route. Those patients who can tolerate large enough doses reap the benefit of a schedule of diuretic therapy which calls for few or no injections.

Dr. Solomon Garb: Is there any significant advantage in giving ammonium chloride with the mercurial diuretic?

Dr. Gold: The answer is yes and no, depending on the amount of mercurial and on the other therapeutic elements in the regimen of treatment. In a human assay experiment with ambulant patients in congestive failure we found that an intramuscular dose of 1 cc. of Mercuhydrin has the effect of about 2 cc. when the patient has been treated with ammonium chloride. That clearly shows an advantage in the use of ammonium chloride. However, when we treat patients with careful salt restriction and liberal water intake, and a daily dose of 2 cc. of Mercuhydrin, we obtain diuretic effects as a rule which are not enhanced by the addition of ammonium chloride. It seems therefore that when a ceiling diuretic response is obtained through the rest of the regimen, it cannot be significantly boosted by the addition of ammonium chloride. For that reason we have given up the use of ammonium chloride in the routine treatment of congestive failure.

Dr. Reader: Is it necessary to prepare the patient with ammonium chloride before the mercurial is given, or may they be given at the same time?

Dr. Gold: It is said that the ammonium chloride for its best effect should precede by a few days the treatment with the mercurials. In our human assay we treated them for a few days before the dose of Mercuhydrin was given. I am not certain whether pretreatment is important, nor whether the results might not be just the same if the mercurial and the ammonium chloride are taken at the same time.

Dr. Reader: Dr. Gold, are there not times when you would prefer not to use as much as 2 cc. of the mercurial diuretic? Would you mention what conditions would provide a contraindication to the use of a dose as large as 2 cc., if there are such conditions?

Dr. Gold: They are very rare. There are occasional cases of allergic reaction to the mercurial in which a reduction of the dose from 2 to 1 cc., or somewhat less, reduces the intensity of the reaction to the point where the drug can still be continued. I refer to a rash, a febrile response, itch, or muscle cramps. The vast majority of patients can tolerate 2 cc. quite well.

Dr. Luckey: Would you comment about the patient who is beginning to lose responsiveness to the mercurials? Does ammonium chloride increase the diuresis significantly from 2 cc. of the mercurial in such a patient?

Dr. Gold: I have taken advantage of many opportunities to add ammonium chloride to the treatment regimen which involved very low salt intake, liberal water intake, and a daily dose of 2 cc. of Mercuhydrin. I don't believe that I have ever seen a patient who no longer responded to this regimen develop diuresis as the result of ammonium chloride. In some of these I have increased the dose of the mercurial to 3 cc. in order to secure the maximum effect possible with doses that are still safe.

Dr. Luckey: I believe that we have seen a few cases in which ammonium chloride enhanced the diuretic response. There are of course many instances reported in the litera-

ture of hypochloremic alkalosis which is occasionally
cause for the refractory state. Responsiveness is restored
the administration of ammonium chloride. Because some
gree of hypochloremic alkalosis is very common in the co
of daily mercurial diuresis, we have taken the position
it is wise to give ammonium chloride to prevent the deve
ment of hypochloremic alkalosis. I do not believe tha
significantly contributes to the diuretic effect in most patie

Dr. Modell: Isn't the refractoriness to mercurial diure
as the result of hypochloremia a special case in that not
ammonium chloride but sodium chloride will abolish
refractoriness? The synergistic action of ammonium chlo
and the mercurial is a different matter.

Dr. Luckey: Yes, that is correct. In regard to the combi
action of ammonium chloride and the mercurial, it is
recollection that the two together produce greater diur
effect than is to be expected from the sum of their effects
separately, namely, potentiation.

Dr. Gold: I seem to recall that the effect is the
verse: less effect from the combination than from the s
of the individual effects.

Dr. Luckey: I saw a definite statement to the effect
there is potentiation in a paper of yours I just read this af
noon.

Dr. Gold: See, you know my paper better than I do. I
forgotten that point.

Dr. Reader: I wonder if Dr. Pitts would care to comm
on the combined action of ammonium chloride and the m
curial diuretic?

Dr. Robert F. Pitts: I have no evidence derived fr
direct clinical use, but what there is points strongly to
fact that the diuretic action of the mercury is more or
specifically related to the reabsorption of the chloride
rather than the sodium ion. In the presence of a hy
chloremic alkalosis the mercurial diuretic may be somew
less effective, inasmuch as there is less chloride in the bo

chloride, by elevating the chloride level to normal or above, potentiates the action of the mercurial diuretic.

Dr. Howard Eder: Several years ago Dr. Wood in our laboratory studied the question of potentiation by ammonium chloride. The ammonium chloride gives rise to an acidosis in the first few days which is then compensated for, and he found that it was not the acidosis but the chloride level which determined the potentiation. The response was equally satisfactory independent of the degree of acidosis

Dr. McKeen Cattell: On that basis, theoretically then, sodium chloride ought to be equally effective.

Dr. Pitts: The trouble there is that you would be adding a great deal of sodium which is unfavorable in edema, whereas with ammonium chloride there is no added cation. It is merely a matter of converting the bicarbonate to chloride. I think it is more reasonable to give the ammonium chloride from the therapeutic standpoint.

Dr. Luckey: In one of the recent issues of *The New York State Journal of Medicine* there is described the cumulative experience of giving 3 Gm of sodium chloride a day during the administration of mercurial diuretics, with the thought in mind of enhancing the diuretic response. It does not seem to me to be a very sound approach to the problem

Dr. Gold With regard to ammonium chloride, it is not an uncommon practice to try a daily dose of 3 Gm. in the endeavor to reduce the number of mercurial injections that need to be given. What I see of this practice does not speak well for it. The milder cases of congestive failure get along equally well without it, and in the more unstable cases the ammonium chloride seems not to be sufficiently effectual.

Dr. Reader. I presume you think it is not worth using because better results can be achieved by simply shortening the interval between the doses of the mercurial diuretic.

Dr. Gold That is it The addition of ammonium chloride complicates the regimen and seems in the end to leave us no better off.

Dr. Reader Before we go on, could I ask Dr. Luckey

about the 2 cc dose of the mercurial Do you agree with Dr Gold that the 2 cc dosage level is perfectly safe and that there are no special situations in which it should be avoided?

Dr Luckey I would agree with that

Dr Reader I wonder if Dr Modell would tell us something about the relative effectiveness of the intravenous and intramuscular routes for the mercurial

Dr Modell There is no material difference between them as measured by the total diuresis in 24 hours The injections were all given intravenously in the early days The intramuscular injection was too irritating with the materials which were then available Mercuhydrin was the first among the group with local irritant action sufficiently low to make the intramuscular route acceptable This route became increasingly popular as the reports in the literature brought to light severe toxicity and deaths from the intravenous injection of organic mercurials

Dr Rinzler The intramuscular route appears to be the one usually used for Mercuhydrin and I wonder if we could have something more about the subcutaneous route The technic is simpler and the patient is apt to be better equipped to make his own subcutaneous injection than his own intramuscular injection Is the diuretic effect the same?

Dr Modell Yes the effectiveness of the subcutaneous injection is the same as the intramuscular injection The subcutaneous route should be used in those patients in whom it is tolerated without inordinately unpleasant local irritation It is especially important for those patients who make their own injections or those who have a visiting nurse or a member of the family do it for them The injection should be made directly under the skin and not into the subcutaneous fat Some of these cause less discomfort than the intramuscular injection

Thiomerin is an organic mercurial diuretic which has come into considerable prominence for subcutaneous injection It was at first believed that it was free of local irritation and while a great many patients can take it without

local effects, long experience has fairly well established the fact that in a great many, local irritant effects with pain, inflammation, and lumps are produced.

Dr. Reader: Which do you prefer?

Dr. Modell: I would use the material that causes the patient the least discomfort I try Mercuhydrin first. If unpleasant local effects occur, I turn to Thiomerin. Sometimes one avoids the local irritation by changing the preparation.

Dr. Reader: I had the impression that Thiomerin was not quite as effective as Mercuhydrin and that its diuretic effects were somewhat delayed.

Dr. Modell: I am not certain that there is any important difference in these respects I might mention that Mercuhydrin costs less and that the preparation is stable, while Thiomerin undergoes deterioration with the formation of irritant materials Dr Gold, do you know of any significant difference in the potency of Thiomerin and Mercuhydrin?

Dr Gold: In bio assay in ambulant patients with congestive failure there is no important difference in their diuretic potency in terms of cc of solution

Dr Reader Have you a comment, Dr Kramer?

Dr Milton Kramer I would like to ask Dr Gold a question having a bearing on the excretion of the mercury and the cumulation of mercury in the course of treatment with the mercurial diuretics How much danger of that is there? The work of Dr Burch with tagged radioactive mercury seems to indicate that under some circumstances, usually some impairment of renal function, the mercury may not be excreted as promptly, even in the presence of a satisfactory diuresis, and that the excretion of mercury may go on over a period of a week or longer, after one injection It would seem reasonable to infer from this that the repeated injection of the mercurial may lead to retention of mercury under conditions which cannot always be defined in advance I wonder whether Dr Gold thinks that these findings should modify or place any restrictions on the intensive routine which he has advocated

Dr. Gold No, I think not The chief reason is that the

intensive system of administration of the mercurials to wh you refer is really a very brief course of treatment It rarely a long drawn out process It is really the misuse this regimen that leads to a long drawn out course of tr ment This so called intensive system calls for a dose of mercurial followed by a diuretic response shown by a loss body weight within 24 hours Each succeeding daily d ought to produce an important loss in body weight By end of about a week as an average for large groups of patie the therapeutic response is complete There are a few whom it occurs earlier, and some who take longer From t point on, the interval between injections is made progressiv longer in accordance with the needs of the particular in vidual for maintaining the "dry state' In a small group patients there remains the necessity for taking an injecti every day, sometimes for the rest of their lives It is a ve small group I don't really know the precise answer to t question of cumulation of mercury in such situations I ha had a few that have gone on 2 and 3 years in that way witho revealing any signs of mercurial toxicity If there has be cumulation of mercury in the kidney, one would have to s that in relation to the doses that are used it causes no har

Dr Cattell Perhaps one would not expect it to be har ful, even if it accumulated, because there is probably a ve large margin of safety Even if the concentration were i creased by 50 per cent, the patient would not be poisone

Dr Gold The margin of safety which Dr Cattell has me tioned is an interesting point The concentration of t mercurial to which the renal cells are exposed during t peak of absorption of any particular dose must be many tim the average concentration during the 24 hour period, a this very high concentration appears not to be harmful

Dr Eder I would like to ask Dr Gold by what criter one would judge whether the mercurial was causing injur It may well be that in terms of frank uremia one may n detect any toxicity, but if one were to look for depressio of renal clearances one might possibly find that more ofte I don t know whether any such studies have been made

patients receiving mercurials over long periods of time It certainly would be a more sensitive method for detection of injury

Dr Gold I am quite sure this is an appropriate question I am also sure we do not have a definitive answer to it at the moment There is an answer, in a way, namely, the fact that some of these patients who appear at the beginning with a high blood urea nitrogen show decline of the nitrogen to normal values which may persist during the ensuing years of treatment There is also the fact that some of these patients with congestive failure are nearly moribund at the time they come under treatment Their failure is brought under control and by an appropriate system of maintenance they carry on for a few years in a fairly active manner If the mercurial is doing any harm during this period when it is managing to keep them alive and in fairly good condi tion we have at the moment no way of finding that out It seems to me that were we to discover a falling off of urea clearance in any of these patients with congestive failure during the use of the mercurial we would probably have to continue to use it just the same since the clinical course shows that it is sustaining their lives

Dr Reader Dr Gold would it not be desirable to dis continue the mercurial in a patient who has become refractory to it in high doses regardless of whether it injures the kidney or not?

Dr Gold The answer should be self-evident but strangely enough it is not always so No medications should be con tinued if they seem not to be doing the patient any good There is no excuse for giving an injection for 2 or 3 weeks to a patient who shows no therapeutic response When the mercurial is effective it shows it by a loss of body weight within the first 24 hours and if no distinct response is present within 2 or 3 days the whole regimen should be re-evaluated

Dr Reader That is the point I had hoped you would bring out

Dr Albert I Rubin You might be interested in know ing of our results with Diamox in a series of 8 or 9 patients

with refractory heart failure whom we studied at Bellevue Hospital. After mercurials failed, Diamox itself was of little use as a diuretic agent. It became very useful *by itself* and in combination with ammonium chloride in producing a hyperchloremic acidosis and setting up response to the organic mercurial to which the patient had previously ceased to respond. This result occurred without exception in these patients. Occasionally the effect of this combination was dramatic. As Dr. Modell has indicated, Diamox is an inhibitor of carbonic anhydrase which is essential for the absorption of bicarbonate by the tubule. As a result, bicarbonate is excreted in the urine and is attended by increased excre tion of sodium as well as potassium. The urine become alkaline. The blood serum chlorides are elevated, carbon dioxide falls, so also the pH. Ammonium chloride potentiate this hyperchloremic acidosis. In this experience which cited, we found that patients whose serum chloride values are normal and who show very little diuretic response to Diamox itself, regain a very satisfactory response to the organic mer curial when the serum chlorides have been elevated to super normal values by Diamox and by Diamox in combination with ammonium chloride. This is a useful treatment. The combination of Diamox and ammonium chloride is more effective in producing hyperchloremic acidosis than either drug alone.

Dr. Reader: Dr. Modell, would you take the position tha the mercurial diuretics are the only ones worth while con sidering in practical management? I am referring to those other materials which you mentioned, ion exchange resins xanthines, ammonium chloride.

Dr. Modell: I think that, just as Dr. Gold has made clear, wherever mercurials can be tolerated, they represent the simplest solution to the problem. The other materials may be considered when the problem cannot be solved by adjusting the doses of mercurial, but they all have disadvantages that justify their being left for last. The ion exchange resins should be included here. I am not sure what the ultimate position of Diamox will be. It has proved itself an effective

diuretic in my own limited experience There is still much to be learned about its toxicity and long term utility

Visitor If a patient develops a hypersensitivity reaction to one of the mercurial diuretics what is the chance of escaping it by shifting to another member of the group?

Dr Modell There is no rule Some patients are allergic to all of them, some to one and not to another of the organic mercurials The patient who has shown an allergic response to a dose of an organic mercurial should be carefully tested for sensitivity to the others before the whole group is abandoned

Visitor What do you mean by testing them carefully?

Dr Modell Give as an initial injection a very small dose, 0 25 cc or 0 5 cc The severity of the reaction depends upon the dose

Dr Reader It might be mentioned that among the side effects the injection of a mercurial diuretic may cause a fever This effect has occasionally been overlooked and such patients have continued to receive regular injections the fever being viewed as a case of malaria

Dr Gold I might amplify your point on fever Dr Reader If one watches the patient closely for febrile reactions one sometimes prevents serious trouble Some of these patients develop no fever with the early doses and then acquire a sensitivity which shows itself by a febrile peak of 1 or 2 degrees This early effect is very often overlooked or interpreted as being due to some intercurrent infection If the drug is continued the febrile reactions become more severe and may be associated with chills erythematous eruption, pain in the muscles and ulcerative stomatitis A sudden spike of fever in a patient receiving an organic mercurial should always be viewed with suspicion as an allergic reaction It is always well to interrupt the injections If it is that it will disappear in about 12 hours or less in the milder grades

Dr Garb Potassium citrate was at one time used as a diuretic Is it any more?

Dr Modell Potassium salts exert a diuretic action but they are seldom used now

Dr. Gold: I think the urologist makes use of potassium citrate.

Dr. Garb: Do you think it is as effective as ammonium chloride?

Dr. Modell: I don't know. I don't think it has ever been assayed.

Dr. Reader: Dr. Luckey, aside from the use of Diamox, are there any devices that you can suggest for managing the patient who has become refractory and does not respond to the intensive regimen of Dr. Gold?

Dr. Luckey: Let me say right off that the mercurial diuretics are so effective in the ordinary run of patients that there is nothing on the scene to take their place. In a practical way, however, we do have the problem of the patient who has become refractory to the mercurial diuretic, and that is the reason for our present enthusiasm for the Diamox story. The two drugs should not be given together, for in that case there seems to be a blockage of the effects of one by the other, and the satisfactory results are only seen when their administration is staggered. These patients that we studied were refractory to all the conventional measures, including Southey tubes and ion exchange resins. Nothing that we have ever done has proved as effectual as the Diamox method of elevating the plasma chloride level. It should be emphasized, however, that the first thing to do when refractoriness appears is to reassess the whole situation for a possible cause: Are digitalis and the mercurials being properly used? Is there too much salt in the diet? Does the patient have a hyperthyroid state, an infection, or constrictive pericarditis? Useful suggestions for treatment may emerge out of these considerations.

Dr. Modell: I would like to ask Dr. Luckey whether he has ever found a patient responding to another mercurial diuretic when he ceased to respond to Mercuhydrin. This is just an example of the idea of shifting from one mercurial to another.

Dr. Luckey: No, when they fail to respond to one, they fail to respond to the others. Nor have I ever found that changing the route of administration has any effect.

Dr. Modell: You mean it does not matter whether the material is given intramuscularly or intravenously, the refractoriness is the same.

Dr. Reader: I think our time is up.

SUMMARY

Dr. Gold: The list of useful diuretic agents is contracting at one end and expanding slowly at the other. The fairly sizeable group of diuretic agents that are usually listed in discussions of this subject, it was indicated, should be presented mainly for historical interest and for possibilities of diuretic effects in very special situations where the most effective agents for one reason or another cannot be applied. It is clear from the discussion in the conference this afternoon that the mercurial diuretics stand almost alone as diuretic agents of major importance in the control of congestive failure and in other situations requiring intensive diuretic actions The details of the use of these agents, dosage, routes of administration, toxic effects, combination with ammonium chloride, relative potency of various preparations, were elaborated Special mention was made of Neohydrin as the most efficient of the oral diuretics of the mercurial group The new oral nonmercurial diuretic, Diamox, *appears to offer promise as the sole diuretic agent in* the milder cases and as a means of restoring responsiveness to the mercurials in refractory cases The details of this important observation and its mechanism are discussed The point was made that ammonium chloride is unnecessary in an appropriately adjusted regimen of failure therapy including injections of an organic mercurial, and that the addition of ammonium chloride only complicates the treatment. There were alternate suggestions for the place of ammonium chloride in diuretic therapy Other items of interest include the perennial question of renal injury by the mercurials and the effect of this possibility on plans of treatment, and means of detecting allergic responses before serious reactions occur

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Most Effective Application of Therapeutic Measures in the Management of Congestive Failure

Dr Harry Gold The treatment of the heart diseases has advanced along several fronts in recent years Surgical transformations in congenital heart disease and surgical repair of acquired heart disease have provided many dramatic developments They have attracted the most attention in reviews of progress and have tended somewhat to eclipse the general interest in an area of progress which may in a sense be considered more important because the developments here involve the lives of much greater numbers I refer to the advances which have taken place in the management of congestive failure, a disturbance of the heart and circulation which causes serious disability in about 30 per cent of the cardiac population The evolution here has been more gradual but no less substantial The patient with suffocation at rest, shortness of breath on the slightest exertion massive swelling of the legs, and such other symptoms as are commonly associated with advanced congestive failure used to dominate the scene in the doctor s office, and the medical and cardiac clinics They are still there, but their numbers are rapidly dwindling What has brought this change about is the subject of the conference today Dr Hugh Luckey will tell us something about it

Dr E Hugh Luckey I should like first to define the condition At first sight it would seem a simple matter to define congestive heart failure In actual fact it is very difficult to find a definition which is not an oversimplification and does not leave important segments out of consideration The best I

can do is to say that congestive heart failure is the result of a primary failure of the heart to maintain the proper blood flow and pressure relationships in the vascular system and that this brings about a disturbance in the volume and distribution of blood with increase in the volume of extracellular fluid. The primary defect, therefore, is impaired cardiac function. The ultimate result is disturbed renal function with salt and water retention. It is the latter which accounts for many of the subjective and the objective features of congestive failure. The edema is one of the important factors in the respiratory difficulty. Congestion of the liver is the most prominent cause of the abdominal discomfort. An increase of the inflow load to the heart incident to the large blood volume completes the vicious cycle.

The measures that are used for the most effective management of this state fall into two groups: 1) those directed toward the heart, the primary site of the difficulty; and 2) those directed toward the secondary factor, the edema.

Any orderly approach to the management of congestive failure requires a consideration of the fact that most of these patients present an immediate precipitating factor of some type. It may be an infection of a general nature or a specific infection of the heart itself It may be some unusual physical or mental exertion or some metabolic disturbance such as hyperthyroidism which brings about an unusual demand for cardiac work The discovery of the precipitating factor in a particular case is manifestly desirable to insure the best treatment

In the direct approach, physical rest is a factor of the first importance This may mean rest in bed, although the bed is not always desirable The patient should be in that position in which he obtains the optimum rest. Sitting in a comfortable chair is sometimes preferable to the bed.

Digitalis still remains the most useful agent for the purpose of securing the maximum cardiac function The selection of a member of the digitalis group and its proper administration is the most vital measure in the treatment of the patient with congestive failure.

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There are special varieties of congestive failure, such as the case of acute pulmonary edema, which require special consideration but which I believe we do not have sufficient time to go into at this time I should like to direct my remarks chiefly to the manner of treating the more usual type, or the so called average patient with congestive failure This might be represented by a 50 year old man with a long standing history of hypertension, with recent symptoms suggesting coronary insufficiency During recent months he has noted a decreasing capacity for exertion, and now, in association with a mild respiratory infection, he develops severe dyspnea orthopnea, swelling of the ankles, and such other features as are commonly related to the state of congestive failure The cardiac rhythm may be normal

While it is possible to carry out the regimen of treatment in the home, it is usually preferable to initiate treatment with the patient under observation in the hospital

With bed rest alone and the elimination of precipitating factors such as infection, a proportion of these patients have a diuresis and recover from the congestive failure In others, however, the failure persists and is brought under control only after various measures are applied I have already mentioned the matter of digitalization Sodium restriction is another measure of much importance The patient with heart failure has an altered capacity to handle sodium The ordinary ward diet contains an amount of sodium corresponding to from 3 to 6 Gm of sodium chloride The average patient with congestive failure tends to retain some sodium on such a diet It is therefore necessary to restrict sodium The dietary intake of sodium chloride can be reduced to about 1 5 Gm with foods that are commonly available in most hospitals by a relatively simple system of selection The object is to allow an adequate caloric intake in a diet as palatable as possible in order to avoid adding to the patient's total discomforts We do not consider it necessary to put in effect extreme restrictions in sodium as are sometimes recommended, since we find that it is unnecessary in the average patient with heart failure Where more extreme sodium

restriction is necessary, restriction to a sodium intake of only 2 to 7 milliequivalents we have usually found it convenient to change to the rice diet since this diet is a fairly standard item in hospitals

We do not look upon milk as a satisfactory initial diet in these patients Most adults are relatively intolerant of milk These patients will often present as their primary complaint the fact that all they have in their diet is milk They would like to have more food to eat There is also the fact that milk is not a low salt food when compared with other low salt foods The intake of salt is low on a milk diet because the calories are so restricted If one were to give a milk diet representing the basal caloric requirement of 25 calories per Kg of body weight the patient would be receiving from 2 5 to 3 Gm of sodium chloride

There seems to be a controversy about water restriction but I think it is not justified Views concerning water intake have advocates at both extremes There are those who have urged marked water restriction and those who have recommended huge amounts of water 6 to 7 liters a day as in the Schemm regimen It seems to me that the results have not been materially different and it is likely that when such opposite practices yield the same results the consideration of water does not have the importance that is assumed to it Retention of water in the patient with heart failure is not a primary difficulty Retention of sodium is primary The patient with heart failure often eliminates water quite promptly It is our view that the patient should be allowed as much water as is indicated by his thirst We do not attempt to maintain the water intake at a high level We leave it entirely to the patient In the patient with congestive failure there is no evidence that we change the rate of glomerular filtration by the use of large quantities of water and there is indication that in most patients the renal function is adequate to maintain a satisfactory urine flow for adequate elimination of metabolites

This regimen of restricted physical activity, adequate digitalization moderate restriction of salt and water [illegible]

result in sufficient diuresis in a number of patients I have had some difficulty deciding how large a number Some years ago, Dr Henry Christian pointed out that such a plan of treatment did not in his experience result in complete elimination of edema in most patients That has also been our experience Because of the fact that recovery has been incomplete and relatively slow, another factor has been added to the regimen of treatment I think this factor is largely responsible for the improved outlook in the management of patients with congestive failure, which Dr Gold mentioned at the beginning I refer to the use of a potent mercurial diuretic These agents act on the kidney directly to promote the elimination of salt and water There has been some question as to how often they should be given The recommendation for the use of the daily dose of the mercurial has stirred up a controversy About 5 years ago a study was carried out at Bellevue Hospital to look into the possible dangers in the daily use of the mercurial Over fifty patients were given a daily dose and carefully studied from the standpoint of electrolyte disturbances There was only one instance with indications that the rapid diuresis might have caused some trouble I say 'might' because even in this case there were other factors which could have been responsible The results were good No marked electrolyte imbalance was encountered Recovery was prompt This study led us to the conclusion that the use of the daily dose of the mercurial, together with other measures which I have mentioned is a safe procedure and results in an improvement in the majority of patients with congestive failure

It is our view, however, that the daily mercurial injection is not necessary in a majority of patients after the first few days In the study to which I referred, we found that as the urine volume was decreasing and the patient's weight was leveling off, there was a tendency for some elevation of the blood urea nitrogen and for the appearance of complaints of weakness It seemed to us that we might have gone past the point of optimum weight and that excessive dehydration might have taken place We have therefore adopted the plan of giving the mercurial diuretics daily only for the first 3

or 4 days in the initial phase of management, and then spread the interval between the injections This probably prolongs somewhat the total period for recovery, but I believe that in this way we are more likely to reach the point of optimum body weight with less chance of going beyond that

I think one cannot emphasize too strongly the importance of daily weighing of the patient as a measure of the efficacy of the treatment in removing edema fluid When the body weight begins to increase it does not necessarily call for an increase in the frequency of the dose of the mercurial but rather for an examination of the whole therapeutic regimen This should include a re-evaluation of the diet as well as of the adequacy of the digitalization

We have had some experience with the resins in the management of these patients Their only advantage that we are able to see is that of decreasing the frequency of the mercurial diuretics This does not seem to be much of an advantage since it is so simple to use the mercurial diuretics Patients can inject preparations subcutaneously themselves at home during the period of maintenance Furthermore we have not been impressed with the usefulness of the resins in patients with the refractory form of heart failure

I should like to spend the last few minutes on the subject of the refractory state of heart failure Much has been written on the point that electrolyte imbalance often accounts for the refractoriness This is infrequent I am inclined to believe that the reverse is the case and that electrolyte imbalance is produced in the course of the treatment of refractory heart failure A case in point is that of the patient in advanced heart failure with anasarca and normal electrolyte concentrations who has been on extreme salt restriction and has become completely unresponsive to the mercurials Such patients have then been treated with resins and we have observed that during such treatment a hyponatremia was produced with no change in the patient's body weight Most patients of this type will not have a diuresis when the plasma sodium is elevated to normal although this does in occasional patients return to the responsive state

We believe that most cases of refractory heart failure will

result in sufficient diuresis in a number of patients. I have had some difficulty deciding how large a number. Some years ago, Dr. Henry Christian pointed out that such a plan of treatment did not in his experience result in complete elimination of edema in most patients. That has also been our experience. Because of the fact that recovery has been incomplete and relatively slow, another factor has been added to the regimen of treatment. I think this factor is largely responsible for the improved outlook in the management of patients with congestive failure, which Dr. Gold mentioned at the beginning. I refer to the use of a potent mercurial diuretic. These agents act on the kidney directly to promote the elimination of salt and water. There has been some question as to how often they should be given. The recommendation for the use of the daily dose of the mercurial has stirred up a controversy. About 5 years ago a study was carried out at Bellevue Hospital to look into the possible dangers in the daily use of the mercurial. Over fifty patients were given a daily dose and carefully studied from the standpoint of electrolyte disturbances. There was only one instance with indications that the rapid diuresis might have caused some trouble. I say "might" because even in this case there were other factors which could have been responsible. The results were good. No marked electrolyte imbalance was encountered. Recovery was prompt. This study led us to the conclusion that the use of the daily dose of the mercurial, together with other measures which I have mentioned, is a safe procedure and results in an improvement in the majority of patients with congestive failure.

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be found to fall into two groups There is the group in which the heart disease has progressed to a point where cardiac output has fallen to a point inadequate to maintain sufficient renal function This is the terminal phase in the natural history of the heart disease There is the other group in which one may have failed to recognize associated and complicating factors which may be brought under control One cannot overemphasize the importance of thyrotoxicosis in this respect Constrictive pericarditis is one of the conditions which is often overlooked Primary hepatic or renal disease not uncommonly complicates the picture One should, of course, mention the fact that before the patient is regarded as truly refractory, it is imperative to examine and re examine the total regimen of treatment to insure that the various measures have been adequately applied

Finally, a few words about two of the complications that arise in the course of the management of congestive failure namely, hypochloremic alkalosis and the low sodium syndrome In the majority of patients with heart failure who develop a diuresis from any cause, the amount of chloride which appears in the urine is high in relation to the sodium loss This produces a hypochloremic alkalosis which is usually of moderate degree and inconsequential, but may be exaggerated in patients who lose huge volumes of fluid, whether this takes place during the use of the mercurial or in association with any other measures This phenomenon has been observed in patients who showed a marked diuresis with digitalis and bed rest alone We have observed it in one patient whose failure was associated with a malnutritional state, in whom a diuresis occurred from bed rest and a nutritious diet alone Some of these patients show only slight change in the plasma chloride level In others, an extraordinary fall in blood plasma chlorides takes place and it does so unpredictably Because of the frequency of such a response, we advocate the use of ammonium chloride in doses of 4 to 6 Gm by mouth during the period of the most marked diuresis in the treatment of congestive failure This recom

mendation is made not for the purpose of potentiating the diuretic effect of other agents but for its value in replacing chloride

Much has been written about the low sodium syndrome It is most commonly encountered in patients in the terminal stages of heart failure The treatment of this condition presents something of a problem When we encounter it, we attempt to correct it by giving the patient salt by mouth or small amounts of hypertonic saline by intravenous injection if the patient cannot take material by mouth I must say that we have not been impressed with the character of the improvement which results from the administration of sodium chloride in these patients However, we do attempt to correct hyponatremia when it is detected

Dr Gold It is pleasant to find Dr Luckey's experience in general agreement with the formulation of the treatment of congestive failure which we published several years ago You have probably become aware of some points of divergence, and perhaps this is a good time to see how some of the disagreements have come about

In order to get the discussion under way I should like to refer back to a few of these points With regard to the definition of congestive failure I wonder what Dr Luckey would think about defining it as a metabolic state in which the essential abnormality is an abnormal retention of salt, in consequence of which water is retained and a state of hyperhydration results The primary seat of the trouble lies in a disturbed function of the heart, but there ensue the secondary circulatory changes involving a diminished capacity of the kidney to excrete salt Such a definition does not involve us with the abstruse nature of heart muscle weakness because there are states of extreme heart muscle weakness as after an acute coronary thrombosis, in which the circulatory abnormality is quite different There is no congestive failure There is only peripheral circulatory shock The treatment in this state of extreme heart muscle weakness is quite different from that of congestive failure The definition I propose also helps to direct attention to the center of the objective in

treatment, namely, measures that will help the organism get rid of and stay rid of excess extracellular fluid, salt, and water. With such a formulation as I have proposed, measures for dehydration become the first order of business. This does not eliminate digitalis to increase the contractile power of the heart. I agree with you that it is extremely important. It should be tried in every case, but there is the fact that there are many cases of congestive failure, especially many with a normal sinus rhythm, in which digitalis is not very effectual and in which only after active diuretic medication with salt restriction is the condition brought under control. I myself fancy this formulation of the issues in the therapy of congestive failure over the more conventional one which you described. Since we both seem to be doing pretty much the same sort of thing in treatment, I suppose the difference in definition loses some of its importance.

I wonder if we could have some discussion of Dr. Luckey's practice of letting the patient's call for water decide the issue of how much water the patient will receive during the management of congestive failure. I once discovered that when I let patients do that, they usually took very little water, a total of a glass or two a day of total fluid. This is partly due to the fact that people generally do not drink much water and partly to the fact that the patients seem to be afraid to drink water when they know themselves to be waterlogged. I agree with Dr. Luckey that the outcome is pretty much the same, even if one pays no attention to this item, in the milder cases of congestive failure. There are, however, the occasional cases in whom the success of the treatment is halted in its tracks by inadequate water, but by boosting the water intake the diuretic response is reestablished. It is our practice to order a total fluid intake of from 2000 to 3000 cc. through the fluids in the food and through other fluids, including water. This insures that most patients will be receiving at least what the average normal person takes in the form of available water through free fluids and normal solid food intake. While Schemm has found that treatment with huge quantities of water is sometimes

helpful, we have not encountered any need for that method of approach.

Dr. Luckey agrees that the daily dose of the mercurial is safe and advocates what seems to me a reasonable approach to avoid excessive dehydration by following the period of daily dosage with a period in which the interval between doses is prolonged. I question the wisdom, however, of his limiting the daily dosage to the first two or three days, for, while this will probably do in the majority of milder cases, it will unnecessarily reduce the efficacy of the system in the patient with advanced congestive failure who has about 60 pounds of edema fluid to lose. Is it not wiser to advocate a more elastic plan, as we have done: the use of the daily dose until the body weight reaches close to the "dry level" and then begin to spread the interval? In the majority of cases that will turn out to be only a few days for the milder cases, but may well extend over a period of 2 weeks or even longer in the more severe and advanced cases. Such an approach can only be advantageous. I think that Dr. Luckey will agree that no aspect of this treatment should be arbitrary. The dose of the mercurial, the interval between injections, and the duration of the daily dose should be determined by the response of the individual patient.

Then there is the question of the milk diet. At the beginning of the treatment we advocate 1 glass of milk and 1 glass of water at intervals of an hour alternately for a total of 4 to 6 glasses of each, giving a total of 2 to 3 liters of fluid, and with the larger amount about 1000 calories in the form of milk, representing approximately 1.5 Gm. of salt. Dr. Luckey does not look upon milk as a satisfactory initial diet because, he says, most adults are relatively intolerant of milk, patients complain of not having enough to eat, because milk is not as low-salt a food as many other articles of diet, and because to get low salt intake with milk requires excessive restriction of calories. I wonder about these objections to milk. I have not found most adults intolerant of milk. They seem to tolerate it very well. They don't like it as a steady diet, but then most patients with con-

gestive failure don't require it for more than a period of several days In our series of nearly 150 patients with congestive failure about whom we published several years ago the "dry weight' was reached in an average period of 6 days some shorter, some longer, and right after this we put them on a mixed diet * I find that most patients with advanced congestive failure will tolerate the inconvenience of a milk diet for several days with the prospect ahead of rapid relief from their suffocation and cough There are a few who develop diarrhea or vomit, or who have some psychological obstacle to taking milk In these we use a mixed low salt diet or some modification of the so-called rice diet I do not know whether milk has any special diuretic properties but our turning to milk arose from the fact that low salt diets are not very easy to carry out even in well organized hospitals The patient sometimes calls our attention to the salty taste of some of the food, and it was not at all rare to find that the maid, in following a routine practice had overlooked the special situation and had put the salt cellar on the tray I have no objection to a low salt mixed diet where one can be quite certain that lapses can be prevented I wonder about the practical significance of the position that milk is not a desirable item here because there are foods that have even less salt than milk and that to get a low enough low salt diet with milk requires excessive reduction of calories Dr Luckey referred to the standard caloric requirement of 25 calories per Kg of body weight A patient weighing 70 Kg would, with this formula receive 1750 calories a day Do we want to put a patient who is at complete rest in the initial phase of the treatment of congestive failure on such a high caloric intake? Is it not desirable to reduce the caloric intake to something closer to 1000 calories a day in the early days of treatment? I believe that reduced caloric intake is one of the conventions in the treatment of congestive failure at the start A quart and a half or 1 5 liters of milk a day gives the patient about 1000 calories with an

* *Conf 2 An Optimal Routine for the Management of Congestive Failure" Cornell Conferences on Therapy* Vol III 1948

average salt intake of 1 5 Gm I agree with the point implied by Dr Luckey that it is not desirable to apply starvation in the long term treatment and maintenance of the patient with congestive failure, but the issue of the milk refers only to a period of several days in the vast majority of cases

Perhaps we might have some questions from the audience, and Dr Luckey can then answer them all at one time

Dr Harold E B Pardee I should like to comment on the patient you referred to, who had 60 pounds of edema fluid to lose

Dr Gold Please do

Dr Pardee I am inclined to avoid proceeding too rapidly in getting a patient of that kind free of edema fluid I tend to slow down the process even if I find it possible to get rid of 2 or 3 pounds of weight a day Certain disturbing symptoms appear, such as drowsiness and other discomforts, which may be related to rapid loss of sodium The reactions are not serious, and they are readily corrected by halting the diuretic treatment It seems to me that these patients have to make extensive physiological adjustments when such large quantities of fluid and electrolyte are lost from the body, and it seems to me wise to allow them to make those adjustments gradually

In connection with the general application of the plan of treatment that was outlined I think it is well to bear in mind the fact that congestive failure does not as a rule come on suddenly, and there are a great many patients with diminished cardiac reserve in whom the more usual signs of congestive failure are absent I am not certain that everyone would call them congestive failure, yet they are in congestive failure and present congestion in the lungs, the liver, and other tissues There is no sharp line These early cases often go without treatment It is important to recognize them and apply the newer measures which have been discussed The treatment does not need to be so intensive The patient may not have to be placed at complete rest He may be able to get along with salt restriction alone or with salt restriction and ammonium chloride by mouth

ventricular failure in whom there either was no peripheral edema or in whom the peripheral edema was controlled by diuretics These patients continued to show a low cardiac output Digitalis decreased the pulmonary venous pressure and increased the cardiac output markedly I think that the work of Stead in relation to sodium and water retention has resulted in too much emphasis on this factor in congestive failure and that we are getting back to the heart again

Dr Gold If I understand you correctly what you are saying is that there are patients in congestive failure who when dehydrated by salt restriction and the mercurials alone still continue to show evidence of failure that these patients require digitalis and that more improvement follows digitalization

Dr Cardon That is correct

Dr Gold That simply means that there are many patients who require both digitalis and the mercurial diuretics and salt restriction

Dr Cardon Yes but perhaps digitalization is the most important factor

Dr Gold That digitalis is the most important factor does not follow from the experience you presented To refer to digitalis as more important would require altogether different kind of evidence

Dr Cardon The point I tried to make is that without digitalization without this effect on the heart one can demonstrate that the state of congestive failure still exists physiologically

Dr Gold Again then what you say is that patients in congestive failure need digitalis

Dr Cardon Yes and perhaps that digitalization may do the job without the mercurials

Dr Gold We can of course look at the other side of the story and say that many of these patients do very well without digitalis and with salt restriction and the mercurials alone The fact is that there are both kinds of patients those who do very well with digitalis alone without the diuretics and those who do very well with the diuretics alone without digi

talis I think the only reasonable approach to this situation is to use both measures, as we have advocated in the routine management of congestive failure, since one cannot distinguish these patients in advance Which of these factors the patient can do without may then be determined for each patient in the course of time, and adjustments can then be made accordingly That seems to me to be the most practical approach to the practical problem

Dr Eggleston, would you care to comment on this discussion?

Dr Cary Eggleston I agree in general with the things that have been said All the factors which present themselves in congestive failure have to be taken into consideration in every patient And in the end the kind of treatment depends on the doctor s judgment of their relative importance in the whole picture of the particular patient Moderate restriction in salt is often very important The use of digitalis is paramount in most instances A considerable number of patients if undigitalized and kept at rest in bed and limited in their salt intake, will recover

Dr Mack Lipkin I was intrigued by Dr Luckey s opening remarks concerning the factors which precipitate an attack of congestive failure In a series of patients observed at the Cincinnati General Hospital some years ago a surprisingly large number were found who themselves attributed their attack to a violent, often prolonged emotional upheaval If this is so it would seem to me important to make an attempt in the matter of rest, to achieve not only physical but psychic rest as well

Dr Gold I believe that one cannot emphasize too strongly the importance of the point which Dr Lipkin has just made An emotional upheaval is commonly the factor which precipitates an attack of pulmonary edema [illegible] heart failure in the hypertensive patient This pr[illegible] factor is also frequently seen in patients with [illegible] disease and mitral stenosis Such patients [illegible] satisfactorily with what appears to be [illegible] physical work [illegible] in relation to

develop an attack of pulmonary edema This does not happen to be acute left ventricular failure, but pulmonary edema due to the sudden increase in blood flow through a narrow mitral valve with high pulmonary vascular pressure This is not congestive failure, although it is often referred to as congestive failure *It is not helped by digitalis* Salt restriction and vigorous diuretic therapy are extremely helpful in such cases, both in treating the attack and preventing recurrences It is, therefore, of some practical importance to consider the fact that the trouble may not lie in failing muscle but in mechanical obstruction at the valve Here diuretics help and digitalis does not

May we hear more from you now, Dr. Luckey?

Dr Luckey As to the definition of congestive failure, I believe it is a misdirection of our interest if we do not include in it the heart as the primary site of the difficulty. I think it is a mistake to define it as a metabolic disturbance involving salt and water, because there are other metabolic disturbances in this condition such as oxygen lack and lactic acid acidosis Lactic acidosis may be a very important factor, although it has not been adequately investigated

As to the amount of water the patient receives, I can only repeat our view that it is of no importance in the patient with heart failure who is having a good diuresis There are situations where the patient is not having a diuresis, where the edema persists and the urine volume falls off when the amount of ingested fluid is too small, in which I boost the water intake up to 2 or 3 liters a day In most instances I see no reason for doing more than allowing the patient's thirst to decide the amount of water

Dr Gold There is much to be said for your viewpoint on the definition of congestive failure It certainly seems sound from the standpoint of pathogenesis I question it only from the therapeutic standpoint The patient in congestive failure has edema fairly generalized or dominant in a special area such as the lungs I have proposed directing our attention to the various measures which remove edema pulmonary or peripheral I propose focusing our attention on measures

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talis I think the only reasonable approach to this situation is to use both measures, as we have advocated in the routine management of congestive failure, since one cannot distinguish these patients in advance Which of these factors the patient can do without may then be determined for each patient in the course of time, and adjustments can then be made accordingly That seems to me to be the most practical approach to the practical problem

Dr Eggleston, would you care to comment on this discussion?

Dr Cary Eggleston I agree in general with the things that have been said All the factors which present themselves in congestive failure have to be taken into consideration in every patient And in the end the kind of treatment depends on the doctor's judgment of their relative importance in the whole picture of the particular patient Moderate restriction in salt is often very important The use of digitalis is paramount in most instances A considerable number of patients, if undigitalized and kept at rest in bed and limited in their salt intake, will recover

Dr Mack Lipkin I was intrigued by Dr Luckey s opening remarks concerning the factors which precipitate an attack of congestive failure In a series of patients observed at the Cincinnati General Hospital some years ago a surprisingly large number were found who themselves attributed their attack to a violent, often prolonged emotional upheaval If this is so it would seem to me important to make an attempt in the matter of rest, to achieve not only physical but psychic rest as well

Dr Gold I believe that one cannot emphasize too strongly the importance of the point which Dr Lipkin has just made An emotional upheaval is commonly the factor which precipitates an attack of pulmonary edema with left heart failure in the hypertensive patient This precipitating factor is also frequently seen in patients with rheumatic heart disease and mitral stenosis Such patients often carry on very satisfactorily with what appears to be ample reserve for physical work and then in relation to some emotional upset

develop an attack of pulmonary edema. This does not happen to be acute left ventricular failure but pulmonary edema due to the sudden increase in blood flow through a narrow mitral valve with high pulmonary vascular pressure. This is not congestive failure although it is often referred to as congestive failure. It is not helped by digitalis. Salt restriction and vigorous diuretic therapy are extremely helpful in such cases both in treating the attack and preventing recurrences. It is therefore of some practical importance to consider the fact that the trouble may not lie in failing muscle but in mechanical obstruction at the valve. Here diuretics help and digitalis does not.

May we hear more from you now Dr. Luckey?

Dr. Luckey. As to the definition of congestive failure I believe it is a misdirection of our interest if we do not include in it the heart as the primary site of the difficulty. I think it is a mistake to define it as a metabolic disturbance involving salt and water because there are other metabolic disturbances in this condition such as oxygen lack and lactic acid acidosis. Lactic acidosis may be a very important factor, although it has not been adequately investigated.

As to the amount of water the patient receives I can only repeat our view that it is of no importance in the patient with heart failure who is having a good diuresis. There are situations where the patient is not having a diuresis where the edema persists and the urine volume falls off when the amount of ingested fluid is too small in which I boost the water intake up to 2 or 3 liters a day. In most instances I see no reason *for doing more than allowing the patient's thirst* to decide the amount of water.

Dr. Gold. There is much to be said for your viewpoint on the definition of congestive failure. It certainly seems sound from the standpoint of pathogenesis. I question it only from the therapeutic standpoint. The patient in congestive failure has edema fairly generalized or dominant in a special area such as the lungs. I have proposed directing our attention to the various measures which remove edema pulmonary or peripheral. I propose focusing our attention on measures

very marked diuretic response to a dose of the mercurial the day before, you often find that the first thing he comments about is the fact that he was up all night and did not get a bit of rest. It can be a very stressful experience for the patient to have to call for the bedpan every few minutes.

Dr. Gold: Why not give the dose of the mercurial early in the morning? If you do this, of course, he is not likely to be disturbed so much during the night.

Dr. Cardon: Not exactly, because the effect of the dose often extends on through the night.

Dr. Gold: The fact remains that the patient is there for the treatment of congestive failure, and the inconvenience of being up several times during the night in the first few days is not too big a price to pay for relief from suffocation.

Dr. Cardon: But if the patient is not suffering especially and he is going to be in the hospital a few weeks, it is not necessary to wring the edema out of his legs so rapidly.

Dr. Gold: I suppose we would all agree that it is well not to wring it out too rapidly. I think if one adjusts the system of treatment so as to secure a daily weight loss of no more than 2 or 3 pounds, it is not likely to be too rapid.

SUMMARY

Dr. Gold: The discussion in this conference on the management of congestive failure may be summarized under two headings, one, mechanism, and the other, details of treatment. There are those who cling to the more conventional way of looking upon congestive failure as a condition having its origin in myocardial weakness which results in secondary renal and other effects giving rise to edema and other manifestations having a similar meaning, and in relation to this viewpoint, digitalis to enhance the function of the heart is considered the primary point [illegible] in treatment, salt restriction and diuretic agen[illegible] as adjuvants. [illegible] alternate viewpoint does not [illegible] essential ele[illegible] of this formulation but shifts [illegible] of [illegible] the metabolic disorder, salt [illegible]

case one takes the position that although the salt and water retention is secondary to failure of heart muscle, it often assumes a high degree of autonomy in the clinical syndrome of congestive failure, so that digitalis to strengthen the heart muscle has in some cases relatively little effect in clearing the state of hyperhydration, and the clinical condition is brought under control only by the use of potent diuretic agents The reasons stated for advocating this departure from the conventional view is the belief that the major share of the credit for the marked improvement in the results of the treatment of congestive failure in recent years is to be ascribed to the early and intensive application of measures designed to enhance the excretion of salt and water through salt restriction and active diuretic therapy

There seemed to be no disagreement on the point that patients with congestive failure should be treated with restricted activity, a digitalis preparation, salt restriction in the diet, and diuretic agents Differences of opinion arose chiefly on matters of the details of the application of these measures, but these details are very important and often decisive What is the most appropriate diet for the short term and the long term restriction of salt intake? What are the advantages and disadvantages of milk in the treatment of the acute phase of congestive failure? Should water be restricted or given freely? What decides the amount of fluid the patient should be allowed? How well do patients do with salt restriction and the diuretic agent without digitalis? What is the best dosage plan for the mercurial diuretic? How rapidly should one attempt to clear the patient of edema? These and related questions were the subject of spirited discussion Special attention was paid to the problem of overtreatment, the low salt syndrome the very early case of congestive failure without the usual manifestations and the special problems of the resistant cases

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case one takes the position that although the salt and water retention is secondary to failure of heart muscle it often assumes a high degree of autonomy in the clinical syndrome of congestive failure so that digitalis to strengthen the heart muscle has in some cases relatively little effect in clearing the state of hyperhydration and the clinical condition is brought under control only by the use of potent diuretic agents The reasons stated for advocating this departure from the conventional view is the belief that the major share of the credit for the marked improvement in the results of the treatment of congestive failure in recent years is to be ascribed to the early and intensive application of measures designed to enhance the excretion of salt and water through salt restriction and active diuretic therapy

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many times by practical experience Gross blood of course can be found in the pericardium for short periods of time in rupture of the heart, either traumatic or following a marked infarct or in dissecting aneurysms I will not list the many causes of pericardial effusion

I would like to conclude by summarizing the steps in the management of pericardial effusion When pericardial effusion is suspected, the diagnosis is often quite clear from a combination of physical and laboratory signs In many instances differentiation from cardiac dilatation is quite difficult In these instances angiocardiography offers the most simple and direct means of positive decision When the presence of pericardial effusion is established, the patient should be closely observed for evidences of cardiac compression There is usually greater risk in waiting when signs of compression are present than in a well planned pericardial tap Pericardial aspiration is occasionally indicated for diagnostic purposes even in the absence of signs of compression In most cases a simplified angiocardiographic procedure should be done prior to pericardial tap In our experience the left precordium, some 2 cm within the left border of dullness in the 5th or 6th intercostal space, has been the site of choice for aspiration Other sites include the region between the ensiform cartilage and the left costal margin, and the area at the angle of the left scapula We prefer the left precordium In most of our cases the diagnosis of the cause of the effusion has not been made In our last 9 cases however, there were 5 instances of bloody pericardial fluid with hematocrits from 3 to about 20 In only one patient was there evidence of neoplasm with metastasis as the cause The presumptive diagnosis in the others was tuberculosis, but this was never positively diagnosed either on culture or on the basis of extrapericardial tuberculous disease In most cases of this type with bloody pericardial fluids we have started streptomycin and para aminosalicylic acid during the period when the culture is incubating and then discontinued it following failure to obtain evidence of tuberculosis In cases of acute rheumatic fever with pericarditis there is general

ıgreement that salicylates or ACTH should be administered promptly. This usually results in prompt subsidence of effuions. In purulent pericarditis the present tendency is to treat he patient with antibiotics parenterally without intrapericardial instillation, although this is feasible and has been done on a number of occasions. In the treatment of pericardial effusion with compression, digitalis is indicated in everal types of cases. There are those in whom it is suspected hat some myocardial disease is also present. There are the cases with auricular fibrillation. Four of the last nine patients ve have seen have had auricular fibrillation at some point during their course. It is useful following removal of a large amount of fluid, at which time myocardial dilatation and heart failure may follow. Attempts at diuresis in the setting of acute pericardial effusion are probably ill advised. However, in large effusions with known underlying heart disease, diuresis may result in the removal of pericardial fluid due o a hydropericardium which is part of generalized edema. Patients who have recovered from pericardial effusion should be followed for evidence of constrictive pericarditis, particuarly when the effusion is bloody.

Dr. Reader: After this extremely well organized, complete presentation, there would appear to be little to say, but perhaps there are some questions.

Dr. Harry Gold: I should like to ask you, Dr. Luckey, about a statement I understood you to make at the beginning, to the effect that pericardial effusion most commonly occurs in a setting of generalized edema.

Dr. Luckey: Yes, an increase in the amount of pericardial fluid above the normal is probably most common in patients who have generalized edema as in heart failure. That would be so if we are to include all cases with a volume of fluid above 50 cc.

Dr. Gold: I would agree with that, but I wonder whether it would not be useful to call attention to the fact that the vast majority of those with such small volumes of fluid present no clinical problem of pericardial effusion and are most often beyond the reach of a clinical diagnosis. My

Dr. Luckey: No, I don't believe so. In regard to the proliferative process, there is a good deal of controversy, but I know of no controversy about the exudative phase.

Dr. Modell: How do you feel about it, Dr. Gold?

Dr. Gold: A little more evidence to support the prevailing belief would be useful. The salicylates seem to influence the course of rheumatic effusions in the joints and I presume in other serous parts as well.

Dr. Cattell: There is considerable support for that concept from experimental work. Silver nitrate was injected into the joints of rats, and the changes in volume were studied by immersing the limb in water. Swelling and the development of necrosis were prevented by giving salicylates.

Dr. Reader: I wonder how useful a guide the angiocardiogram is in determining the site of the tap and also in determining how much fluid should be removed? Is it a fairly reliable guide?

Dr. Luckey: I think it is useful in deciding how much cardiac dilatation is present. I don't think it is helpful in deciding where to perform the tap. We have had no difficulty with the anterior precordial approach, and I see no reason to use the other two approaches since this one is so convenient from every standpoint, including the positioning of the patient.

Dr. Reader: In what position do you usually have the patient?

Dr. Luckey: Usually sitting up at about a 70 degree angle.

Dr. Reader: Do you go in perpendicular to the skin?

Dr. Luckey: Yes. I can describe the technic if you would like. First, you have to know your landmarks. Here fluoroscopy is valuable, in association with careful percussion of the cardiac border. As soon as you have found the left cardiac border, auscultate over the area and feel for the apical impulse. This will nearly always be absent at the point where you plan to introduce the needle. Next, make the patient comfortable. Both the patient and the doctor are usually quite excited in this situation, and we give the patient

morphine, about 8 mg., which will often completely relieve apprehension.

Dr. Reader: On the part of the patient?

Dr. Luckey: On the part of the patient.

Dr. Cattell: That doesn't seem fair. Both the patient and the doctor are nervous, so you give the patient morphine and the doctor gets nothing.

Dr. Luckey: A long 18-gauge needle with a short bevel, a 50 cc. syringe with a three-way stopcock intervening between the needle and the syringe, and a rubber side-arm are used. Some have found it helpful to put a 4-inch piece of rubber tubing between the needle and the three-way stopcock to prevent too much movement of the needle from the fatigue tremors of the physician. Then with a 5 cc. syringe and a long 20-gauge needle, the area is prepared with procaine. It is quite common to enter the pericardial sac at the time the area is being prepared and to remove a small amount of fluid. After this the 18-gauge needle is inserted into the parietal pericardium, avoiding the intercostal artery, which is just below the rib, and the internal mammary artery which is some 1.5 to 2 cm. from the external border of the sternum at the fourth and fifth intercostal space. One should be well beyond that point. When the parietal pericardium is entered, it usually feels as if you were puncturing a bladder. The fluid is then removed and collected from the side-arm of the three-way stopcock. At first it usually flows quite freely. Following the removal of as much as is desired, it is sometimes useful to introduce about half the volume of fluid as air to allow more careful x-ray study of the cardiac contour.

Dr. Gold: How much of this do you let the patient see?

Dr. Luckey: In the last case we simply placed a towel over the patient's face.

Dr. Seymour H. Rinzler: Since the widespread use of anticoagulants, there have been some reports of bloody pericardial effusion. Have you seen any?

Dr. Luckey: I don't recall a case of bloody pericardial fluid in myocardial infarction with anticoagulant therapy in the last 6 years.

Dr. Reader: Because it would tend to reduce cardiac output further?

Dr. Luckey: Yes. Dr. Eugene Stead studied a number of instances of pericardial tamponade. I think there were 7 or 8 cases, of which 3, 4, or 5 were due to cardiac rupture from a wound of the heart and 3 to large pericardial effusion. He found that the hemodynamic abnormalities were essentially the same in both groups of patients, with the difference that the venous pressure was considerably higher in the patients with chronic effusion, who also had hypervolemia. This is added evidence that hypervolemia is necessary for some of the increase of venous pressure seen in chronic heart failure. He also found that cardiac output was low when the evidence of progression was quite marked, but that tachycardia with a small stroke volume maintained cardiac output for some time during early compression. Furthermore, peripheral resistance was markedly increased. In some of the patients he tried the administration of fluid and serum albumin despite this marked venous hypertension. Venous pressure rose, cardiac output increased, and arteriolar-venous oxygen difference decreased, suggesting that administration of fluid was actually an advantage in this situation. From that indirect evidence, one would conclude that phlebotomy would do exactly the opposite and would be unwise. At the time of the most recent report from Grady Hospital in Atlanta, Georgia, fluid was given to all patients with cardiac tamponade due to knife wounds when they were first seen. If there was evidence of continued bleeding and tamponade, operation was performed.

Dr. Garb: If you had a patient with congestive failure and some pericardial effusion without compression, and if that patient were then digitalized, would you expect the pericardial effusion to interfere with the normal response to the digitalis?

Dr. Luckey: No, I would not.

Dr. Modell: I'd like to ask Dr. Luckey if there isn't some overemphasis on the hazards of the tap as a diagnostic or as a therapeutic procedure. Even if we assume that occasionally

you go through into the wall of the myocardium, is that such a disaster?

Dr Luckey This point has been brought up a number of times Cardiac punctures for diagnostic purposes are of course done experimentally It is a common procedure to puncture the ventricle of the dog and in a recent report from Cuba this was used as a substitute for cardiac catheterization in congenital heart disease There are instances of bleeding but I think the main danger is not from bleeding from within the cavity, but from nicking one of the coronary vessels which will then bleed I do think the dangers of a tap have been overemphasized

Dr Reader Fatalities have been associated mainly with hitting an artery, either a coronary vessel, the internal mammary, or one of the pericardial vessels

Dr Luckey Some tears of the right ventricle have occurred, and also the left auricular appendage is in such a position that it could be torn by the needle

Dr Cattell I would like to go back to that case you cited because it does not appear to give any evidence that the use of mercurial diuretics and a low salt diet were ineffective With 1000 cc of fluid it seems to me that the heart was most probably under compression, at least, I don t see how you know it was not The fall in the venous pressure, of course, might be due to more than one cause, but it could well have been a contribution from the removal of the fluid

Dr Luckey I suppose that is so We based our opinion largely on the absence of change of the cardiac contour on x ray despite complete removal of the rest of the edema

Dr Cattell Wasn t it only a matter of 2 or 3 days? You could hardly hope to remove any very large volume of fluid in that time

Dr Luckey It was a longer period than that, 2 or 3 weeks

Dr Reader Dr Luckey, one thing that has not been made clear is the question of how often it is necessary to repeat the tap in a patient who has compression

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ferring to had a hemorrhagic fluid from actual involvement of the pericardium.

SUMMARY

Dr. Garb: Only a small fraction of all pericardial effusions require paracentesis. A tap usually is necessary only in the presence of cardiac compression. In that circumstance, it may be life-saving. Cardiac compression is related not only to the size of the effusion but also to its speed of development. Rapidly forming effusions of 500 to 750 cc. may create a clinical problem, while slowly developing effusions of up to 2000 cc. may not. Definite, probable, and possible signs of effusion were described. If there are signs of compression, there is usually greater risk in waiting than in proceeding with a tap. In most cases, a simplified angiocardiograph should be taken before attempting pericardial aspiration. The site of choice and precautions to be observed were thoroughly described. It is not necessary to remove all the effusion. In most cases, digitalization is indicated. The special circumstance of pericardial effusion due to acute rheumatic fever was discussed. Patients who have recovered from pericardial effusion should be followed for evidence of constrictive pericarditis. There seemed to be general agreement that a skillfully performed pericardial tap is not very hazardous. The discussion developed some difference of opinion concerning the value of dehydration therapy in pericardial effusions from various causes. One group was of the opinion that dehydration might be contraindicated. Others felt that this method of treatment might be of benefit to some patients. In each case the arguments were based on analogies because of the absence of direct evidence.

A Re evaluation of Quinidine Therapy

Dr George G Reader We have had a few conferences on quinidine in recent years, but the subject seems to be practically inexhaustible There always remain questions of uses and abuses, indications and contraindications which are in need of further elaboration Such a discussion is of particular importance at the present time in view of the growing interest in substitutes for quinidine Dr Gold will start off the discussion

Dr Harry Gold The subject of quinidine therapy is one of those which can carry themselves along satisfactorily in a conference through the medium of questions and answers I will make a few introductory remarks on the subject for the purpose of getting the discussion under way I believe it is safe to say that quinidine ranks with the great among thera peutic agents It has had a stormy career When it was first introduced for the treatment of auricular fibrillation about 30 years ago the enthusiasm sounded like the end of the problems of treating auricular fibrillation There were items in the newspapers to that effect As you know, that did not turn out to be the case The situation not only changed but reversed itself, and it was not very long before large numbers of observers came to regard quinidine as a dangerous therapeutic agent, some even preferring to avoid it Experience over the years has helped to define more satisfactorily the place of quinidine in therapy of the heart It is now possible to put into effect a plan of treatment which insures the maximum benefit from the drug with the minimum of risk, often a negligible risk By far the majority of patients with premature contractions that are troublesome, parox-

ysms of auricular fibrillation or flutter, paroxysms of auricular or ventricular tachycardia, can count upon satisfactory control on a suitable system of quinidine medication. It is a noteworthy feature of the literature on the efficacy of quinidine that the incidence of satisfactory results differs widely from one observer to another. I believe this is largely a matter of dosage. Dosage is probably the weakest spot in the whole system of quinidine therapy. I should like to make a few remarks about dosage.

Quinidine is a drug which almost invariably produces minor toxic effects before it produces serious effects. In this respect it is much like digitalis; and, therefore, the only proper system of dosage is one in which an appropriate concentration in the body is built up gradually by the cumulation of fractions. The purpose is two-fold. On the one hand, it avoids serious toxicity; and on the other hand, it eliminates fixed upper limits of dosage which greatly restrict the usefulness of quinidine in the more tolerant cases. One sees it stated that if a daily dose of 2 or 3 Gm., or something of the sort, fails to produce the therapeutic results, discontinue it after a period of trial. Such procedure is no more applicable to quinidine therapy than to the case of digitalis therapy. Each individual patient should be treated by a gradual steppage system of increasing dosage, the physician watching more closely at the higher level of dosage for minor toxic effects which call for the cessation of the drug. If one does that, one is certain to include the more resistant cases in therapeutic successes and to avoid serious toxicity.

I might say at this point that the place of quinidine in heart disease relates only to the control of abnormal rhythms. It has nothing to do with the problem of heart failure except in so far as heart failure may be involved indirectly. A person 65 years of age with arteriosclerotic heart disease, when he develops an attack of auricular fibrillation, sometimes goes into congestive failure. Quinidine may prevent the paroxysm, and in that way prevent the congestive failure; but, again, the direct action of the drug relates only to the matter of controlling ectopic rhythms. Quinidine may be regarded

made some years ago we decided that no one ever discovered a reaction from the 3-grain test dose which altered the course of the treatment.*

Dr. Seymour H. Rinzler: Does the dosage of quinidine depend upon the type of arrhythmia? Are the doses larger or smaller for the more or less serious forms of arrhythmia?

Dr. Gold: I don't believe there is any relationship. There are patients with premature contractions which are relatively harmless extra beats, who may be very sensitive or exceedingly resistant to quinidine. The same is true of the more serious forms of ectopic rhythm, ventricular tachycardia. Some patients with ventricular tachycardia are very sensitive and others exceedingly resistant to quinidine. The best technic for answering this question as to whether, for example, ventricular tachycardia requires more or less quinidine than, let us say, premature contractions, has never been applied to the subject, but I believe that if there is a difference, it is not a conspicuous one.

If we look at your question, however, in terms of the gravity of the problem in a particular patient, then we should say that the more severe the paroxysm, the larger the doses and the more intensive the treatment regimen Consider a particular person, 65 years of age, who complains of troublesome premature contractions which give rise to a lump in the throat and some nervousness. At another time this same person may present himself with something else, a paroxysm of auricular fibrillation which has caused marked shortness of breath and edema of the lung. These two situations call for different schedules. In the more serious one, one starts with larger doses and shorter intervals, and is involved in somewhat greater risks of toxicity. In the less urgent situation of premature contractions, one may start with smaller doses and longer intervals, and take one's time eliminating the risk in the endeavor to bring them under control.

Dr. Modell: In building up this concentration, Dr. Gold,

* Conf II, "Uses and Abuses of Quinidine," *Cornell Conferences on Therapy*, Vol. II, 1947.

how do you proceed in relation to the shortening of intervals and to the increase in the size of the individual fractions? What minor toxic symptoms do you look for as indications for interruption of the drug?

Dr. Gold: Let us consider first the situation of a paroxysm of an ectopic rhythm such as paroxysms of auricular tachycardia, one in which the problem is that of prevention. What I usually do in such a case is to start with 0.3 Gm. quinidine sulfate by mouth 3 times a day. I tell the patient to take it until there is another attack. If another attack does not occur, he continues that dosage indefinitely. After another paroxysm, he is instructed to take 2 tablets, 0.6 Gm., 3 times a day. He continues this in the same manner until there is another attack. This calls for an increase in dose and is accomplished by shortening the interval to every 4 hours instead of every 6 hours. It is the appearance of another attack which reveals the need for higher concentrations. I think it is wise to warn the patient that it may take a few months to work out that level of dosage which will ultimately keep him free of attacks. This avoids discouragement. When a daily dosage level around 3 Gm. is reached, it is well to check with the electrocardiogram, made after the total dose for that day, for a prolongation of the QRS time. It begins going up at about that level and sometimes reaches values 50 per cent or more above the normal. In some patients doses as high as 6 Gm. a day are tolerated without this effect, but in others the spreading of the QRS time occurs fairly early. If there has been no change, one can increase the dose by another gram or so a day if there is need for it, again checking with the electrocardiogram daily for evidence that a QRS time of, let us say, 0.08 has gone up to 0.12 or thereabouts.

Dr. Reader: Suppose you find the QRS time has gone up to 0.12 second, do you have to discontinue the quinidine? Will not the depression of intraventricular conduction continue to progress as the doses are continued?

Dr. Gold: The curve of quinidine cumulation with the fixed daily dose tends to level off in 3 to 5 days, so that any

made some years ago we decided that no one ever discovered a reaction from the 3-grain test dose which altered the course of the treatment.*

Dr. Seymour H. Rinzler: Does the dosage of quinidine depend upon the type of arrhythmia? Are the doses larger or smaller for the more or less serious forms of arrhythmia?

Dr. Gold: I don't believe there is any relationship. There are patients with premature contractions which are relatively harmless extra beats, who may be very sensitive or exceedingly resistant to quinidine. The same is true of the more serious forms of ectopic rhythm, ventricular tachycardia. Some patients with ventricular tachycardia are very sensitive and others exceedingly resistant to quinidine. The best technic for answering this question as to whether, for example, ventricular tachycardia requires more or less quinidine than, let us say, premature contractions, has never been applied to the subject, but I believe that if there is a difference, it is not a conspicuous one.

If we look at your question, however, in terms of the gravity of the problem in a particular patient, then we should say that the more severe the paroxysm, the larger the doses and the more intensive the treatment regimen. Consider a particular person, 65 years of age, who complains of troublesome premature contractions which give rise to a lump in the throat and some nervousness. At another time this same person may present himself with something else, a paroxysm of auricular fibrillation which has caused marked shortness of breath and edema of the lung. These two situations call for different schedules. In the more serious one, one starts with larger doses and shorter intervals, and is involved in somewhat greater risks of toxicity. In the less urgent situation of premature contractions, one may start with smaller doses and longer intervals, and take one's time eliminating the risk in the endeavor to bring them under control.

Dr. Modell: In building up this concentration, Dr. Gold,

* Conf. 11, "Uses and Abuses of Quinidine," *Cornell Conferences on Therapy*, Vol. II, 1947.

how do you proceed in relation to the shortening of intervals and to the increase in the size of the individual fractions? What minor toxic symptoms do you look for as indications for interruption of the drug?

Dr Gold Let us consider first the situation of a paroxysm of an ectopic rhythm such as paroxysms of auricular tachy cardia one in which the problem is that of prevention What I usually do in such a case is to start with 0 3 Gm quinidine sulfate by mouth 3 times a day I tell the patient to take it until there is another attack If another attack does not occur, he continues that dosage indefinitely After another paroxysm he is instructed to take 2 tablets 0 6 Gm , 3 times a day He continues this in the same manner until there is another attack This calls for an increase in dose and is ac complished by shortening the interval to every 4 hours instead of every 6 hours It is the appearance of another attack which reveals the need for higher concentrations I think it is wise to warn the patient that it may take a few months to work out that level of dosage which will ultimately keep him free of attacks This avoids discouragement When a daily dosage level around 3 Gm is reached, it is well to check with the electrocardiogram, made after the total dose for that day, for a prolongation of the QRS time It begins going up at about that level and sometimes reaches values 50 per cent or more above the normal In some patients doses as high as 6 Gm a day are tolerated without this effect, but in others the spreading of the QRS time occurs fairly early If there has been no change, one can increase the dose by another gram or so a day if there is need for it again checking with the electrocardiogram daily for evidence that a QRS time of, let us say, 0 08 has gone up to 0 12 or thereabouts

Dr Reader Suppose you find the QRS time has gone up to 0 12 second do you have to discontinue the quinidine? Will not the depression of intraventricular conduction con tinue to progress as the doses are continued?

Dr Gold The curve of quinidine cumulation with the fixed daily dose tends to level off in 3 to 5 days, so that any

large doses, 3 and 4 Gm. daily. One was in a patient with idiopathic thrombocytopenia. Without quinidine, the blood platelet count was about 96,000, and during quinidine action it declined to about 30,000 with the appearance of black and blue marks on the skin. This was repeated several times. It was deemed unwise to try to control the paroxysms of auricular fibrillation under these conditions, and quinidine was discontinued. The other was a fatal case. It was the case of a physician who found it necessary to take 3 to 4 Gm. of quinidine sulfate daily to keep free of paroxysms of auricular fibrillation. After many months on this dosage, he broke out in black and blue marks. Within a few days these increased to a generalized purpuric eruption, and he died in convulsions from what was apparently a cerebral hemorrhage before anything could be done. These two were reactions to large doses and only after prolonged treatment. In the first of these cases I believe we anticipated disaster by the finding of the marked depression in the number of blood platelets. Had we had more blood counts in the second case it is conceivable that disaster might have been averted there also.

Dr. Reader: I think this is the kind of idiosyncrasy in which the reaction is apt to occur abruptly at a dose which is similar to the one which had previously been tolerated well, and that dose does not need to be a large one. It seems to be similar to the situation of thrombocytopenia during the use of hair dyes. It is not a matter of the amount that is used. The reaction appears to come about as the result of some special trigger mechanism. The patient may use the compound for several years without trouble, and then suddenly a reaction occurs.

Dr. Gold: I am still wondering whether one is justified in the position that there is no relationship between the dose and the severity of the reaction, for in the majority of allergic reactions, I believe, the severity of the reaction still depends upon the dose, whether the level of dosage is low or high.

Dr. Luckey: I doubt that doing blood platelet counts is of any value in relation to quinidine therapy because the

rhythms which occur in the process of restoration of a sinus rhythm by means of quinidine may not be the result of the drug at all, but due to the natural tendency for pacemakers in the heart to become inordinately busy when the normal sequence of discharges is interrupted

Dr Reader How about the digitalis problem? Do you usually counsel dropping digitalis when you start quinidine?

Dr Gold Where you can get along without the two drugs together, try to do so This is the policy I pursue I do not know the full extent of the risk I cannot even prove that there is a risk except from animal experiments There the evidence is strong Dr Modell and I published the results of some experiments in dogs several years ago in which it was found possible to produce a variety of serious disorders of cardiac rhythm with cardiac arrest in digitalized animals by doses of quinidine which have no such effects in the absence of digitalis There is something about the synergistic actions of these two agents acting at the same time on heart muscle which gives rise to an effect that is not predictable from the action of either alone How often this occurs in the human situation no one knows The consequences seem to me too serious to try to find out, and so I try to avoid it In some cases it is possible to do so where congestive failure is present by the use of salt restriction and the mercurials instead of digitalis to control the symptoms of failure This allows us to proceed with quinidine as freely as seems necessary A situation like this sometimes arises in connection with ventricular tachycardia with which congestive failure may coexist I do not believe that one should feel free to use as much quinidine as is necessary to control the ventricular tachycardia in such a case if full doses of digitalis are there at the same time for the control of the failure

Dr Reader If the patient with auricular fibrillation has a very rapid ventricular rate, would you be inclined to slow it down by means of digitalis first before you attempt restoration of the normal rhythm with quinidine?

Dr Gold I do not as a rule If the decision is reached that

the particular individual is suitable for an attempt to restore normal rhythm, I proceed with quinidine directly

Dr Modell Is there not a theoretical objection to the use of the two drugs together? Is there not some indication that the actions of the two are antagonistic in relation to the termination of auricular fibrillation?

Dr Gold There is some evidence of antagonism of digitalis and quinidine with respect to the circus movement, but the actions of the two drugs are so complex that the final results cannot be safely predicted, and there are reports of groups of patients in whom auricular fibrillation was successfully terminated by quinidine in patients who were under the effects of digitalis The answer to that question is indecisive

Dr Rinzler If gastrointestinal symptoms appear during the use of quinidine orally, is it possible to proceed at that point by some parenteral method with safety?

Dr Gold Yes, the preparation of quinidine sulfate in propylene glycol is very satisfactory for intramuscular injection It comes in ampules containing 0 2 Gm per cc An intramuscular injection of 0 2 Gm at intervals of 2 or 3 hours deep into the buttock muscles helps to build up an effective concentration I am not sure that this might prove to be the method of choice in terminating a paroxysm of ectopic rhythm It would get around the cases in whom trouble arises as a result of gastrointestinal symptoms

Dr Reader Suppose you have a patient with auricular fibrillation in whom you build up an effective concentration of quinidine and the normal rhythm is thereby restored, do you continue quinidine after that?

Dr Gold That depends The patient's history will sometimes help to decide the matter If the attacks are exceedingly infrequent, one every 2 or 3 years or so, it is more expedient to treat an attack than to attempt prevention by a maintenance system of quinidine On the other hand, if the attacks come daily or at some other intervals which are fairly short, I am likely to place the patient on a maintenance system to prevent recurrences

the patient digitalized with the full realization that a risk is incurred in using large doses of quinidine in the presence of full digitalization The hazard of the treatment is weighed against the hazard of the condition

Dr Modell I would like to point out the fact that the hazards of quinidine in the various disorders of rhythm are not due solely to the toxicity of the drug Is it not a fact that there is an inherent danger in terminating an abnormal rhythm by no matter what drug it is accomplished?

Dr Gold You are quite right Dr Luckey had earlier called attention to the fact that in the transition between the ectopic and the normal rhythm, escape rhythms may reveal themselves which may be very disturbing It is probably an other aspect of the same general problem that after an ectopic rhythm is blotted out the heart may be left without a pace maker for a sufficiently long time to cause disastrous effects This may be the cause of some of the sudden deaths not necessarily the result of drug toxicity but the result of the removal of the ectopic focus which was at the time apparently the only effective pacemaker

Dr Luckey In regard to ventricular tachycardia I think it is well to bear in mind the difference between the two situations one with and one without concomitant A V block If the ventricular tachycardia is the result of an unusually excitable focus in a ventricle, as in some patients with myo cardial infarction quinidine or Pronestil may terminate the paroxysm with satisfactory restoration of a normal rhythm If complete heart block is present, however the abolition of the ventricular tachycardia may leave the heart without a pacemaker the result cardiac standstill It is better to treat ventricular tachycardia in such a patient by other measures

Dr Reader Such as what?

Dr Luckey Digitalis appears to be helpful in some of these It may be by increasing the coronary flow

Dr Gold I would like to suggest an alternate solution to this problem As the majority of cases of ventricular tachy cardia present themselves, we have no means of knowing whether complete heart block co-exists or not In a few cases

I have pursued a plan which I now believe is the method of choice for all cases of ventricular tachycardia The dosage of quinidine is so arranged as to produce progressive slowing of the idioventricular rhythm without aiming at direct abolition of the abnormal rhythm As one follows the condition closely, the ventricular rate may slow from 180 to 140, then down to 110, then to 90, and so on If these changes are followed by means of the electrocardiogram, one will often observe that at the lower rates the normal rhythm has already been established, but not infrequently it is still an idioventricular rhythm even at the very low rates of 60 or 70 a minute, signifying that no active pacemaker other than the focus for the ventricular tachycardia is at the time available in the heart It also happens that if the rate is maintained at the lower levels of 90 or 100 for a day or two, normal beats of sinus rhythm will begin to appear in the electrocardiogram This plan of treatment avoids the risk of leaving the heart without a pacemaker on the abrupt cessation of an ectopic pacemaker There are some physiological experiments which show that a very rapid ectopic rhythm tends to suppress pacemaking in the rest of the heart for a considerable period and that dormant pacemakers become active if the ectopic rhythm is maintained for some time at a slow rate

Dr Reader I think our time is up

SUMMARY

Dr Gold The various aspects of quinidine therapy were explored in this conference types of patients in which it is useful, types of clinical problems to which attention is directed, plans of dosage toxic effects sources of danger, methods for reducing the risks, and such other matters relating to the subject as emerge from extensive experience Quinidine therapy is directed against *only one* aspect of heart disease, namely, disorders of rhythm, and with varying degrees of efficiency is useful in all the auricular and ventricular ectopic rhythms It was pointed out that the treatment

hypotension from hemorrhage Animals anesthetized with ether were even more susceptible to the shock procedure withstanding less blood loss and a shorter period of hypotension to attain the irreversible stage of shock On the contrary, anesthesia with cyclopropane did not have the effects of that with barbiturates or ether The behavior of these animals was more like those not under the influence of barbital or ether anesthesia From the experimental standpoint, therefore, there are here two anesthetic agents barbiturates and ether, which reduce the animal s tolerance to bleeding as such and shorten the period in which the animal sustains vasocompensatory powers against hypotension of a marked degree

In subsequent experiments we examined the behavior of the animal not only during the shock produced by the hemorrhage but during the period of recovery following return of blood pressure to normal levels by transfusion of the blood originally removed In a typical experiment of that kind the dog was bled until the blood pressure declined to shock levels where it was allowed to remain for approximately 4 hours At the end of that time the typical vascular changes of irreversible shock and the diminished precapillary responses to epinephrine appeared in the omentum Small transfusions were sometimes administered to keep the animal alive at this phase of shock We then gave a single large transfusion of the blood previously removed which usually restored the blood pressure to the range of the normal for that animal Prior to the bleeding an intravenous injection of 2 mg of morphine per Kg would produce a transient fall of the blood pressure of approximately 10 to 12 mm of mercury This dose of morphine was repeated in the period following the shock, in which transfusion had boosted the pressure to the normal levels Immediately after the morphine at this time, the animals entered into abrupt vasomotor collapse and died, showing the characteristic changes in the splanchnic arterioles indicative of irreversible shock This reaction was in sharp contrast to that following the dose of morphine prior to the shock state It was as if the state of

shock although it seemed to be terminated as a result of the transfusion had in some way greatly diminished the animal s vasocompensatory ability Similar findings were obtained with subcutaneous injection of morphine This response oc curred regularly after morphine causing death within about 20 minutes in 17 out of 18 animals studied

There are various observations which suggest a counter part of this phenomenon in patients We saw a patient at another hospital who presented a situation which seems quite similar to that I have just described in the dog This was a 42 year-old Puerto Rican woman with carcinoma of the esophagus for which an operation was performed A pre operative injection of Magendie s solution a solution of morphine had no effect upon her blood pressure During the operation there was considerable blood loss and the blood pressure fell markedly She was transfused throughout the operation and received in all 1400 cc of blood The blood pressure gradually returned to normal after a period of 4 hours of severe hypotension About 10 hours after the operation the patient was awake partially sitting up in bed and talking to relatives Because she complained of pain at the operative site she received 15 mg of morphine sub-cutaneously About 20 minutes later she was found in a state of acute vasomotor collapse and died The post mortem ex amination failed to reveal any cause for the sudden return of shock and death Another occasion was observed when through a mistake in the interpretation of orders the patient received a relatively large dose of morphine about 8 hours after the recovery from an operation This patient passed into a state of deep shock She was treated vigorously and subsequently recovered We found in further dog experi ments that at the time of the rapidly falling blood pressure after intravenous injection of morphine in the postshock period if transfusions and pressor agents were employed im mediately the falling of pressure might be arrested and the animal would often recover

The observations of Beecher in the Italian theater of the last war are of importance here He noticed that morphine

low, in the neighborhood of 60, and the pulse rate usually high, above 100 It also helps to have a look at the whole man Such a patient is likely to appear anxious look tired prefer to sleep, and show a state of restlessness associated with a feeling of exhaustion An anesthetic in such a person carries a high risk of producing a profound state of shock Another type of case which may be deceptive is one in which the patient has had a severe wound with bleeding and in whom a normal pressure with fairly normal pulse rate has been established by plasma or a plasma substitute This patient may look fairly well, and the vital signs seem in order An anesthetic in this patient, especially one that decreases the respiration may unmask the low oxygen carrying capacity of his circulating fluid, giving rise to a shock like state due to his inadequate capacity to oxygenate the tissues This leads up to the point that only whole blood should be used to replace hemorrhage Other fluids serve as temporizing measures, but in the end we must have red cells to replace the red cells that have been lost

Other conditions being equal, cyclopropane is the anesthetic agent of choice for the patient in shock This statement needs much qualification, and its full meaning must be viewed in the light of the various conditions which determine the safety of anesthesia From the standpoint of their effect on the patient in shock there is probably little difference between cyclopropane, ether, and Pentothal in extremely light planes of anesthesia Their differences become quite apparent when the anesthesia is deep In such a case cyclopropane is by far the most favorable ether next and then the barbiturates It has been our experience here, and it is confirmed by experience around the country, that cyclopropane is the anesthetic agent of choice in one who has had a massive hemorrhage or in whom considerable blood loss is anticipated

The anesthetic agents not only affect the peripheral vascular mechanism but also the respiratory mechanism some being respiratory depressants and others stimulants In this connection the experience of the anesthetist is of great im

portance It does little good to order cyclopropane anesthesia to be given by one who has had little experience with it If his experience relates more to the administration of ether an ether anesthesia for the patient in shock is likely to be more satisfactory in his hands than cyclopropane for if he is unfamiliar with cyclopropane he may induce respiratory depression with its associated respiratory acidosis and cardiovascular irregularities The same is true of Pentothal anesthesia Even though it is less favorable than cyclopropane the person who has had more experience in its use than with cyclopropane is likely to find the Pentothal preferable for his anesthesia in the patient in shock

Dr Reader Thank you Dr Artusio Are there any questions?

Dr Gerald M Silverman Could we have an answer to this question relating to the specific case of gastrointestinal bleeding from say suspected duodenal ulcer? This patient arrives with his blood pressure down to shock levels and he is apprehensive In regard to the admission orders the question arises as to how best to relieve the apprehension Should we or should we not give something like phenobarbital or morphine?

Dr Reader Dr Cliffton what do you customarily do with patients who are admitted with gastrointestinal hemorrhage?

Dr Eugene E Cliffton It depends If there has just been some bleeding and the patient is not on the verge of shock then morphine is a very proper medication and relieves the apprehension perhaps better than any other drug we have at the present time However in the case of shock due to hemorrhage from the bleeding ulcer or from war wounds or anything else morphine is likely to increase the state of shock

Dr Harry Gold The point that decides the issue then is the doctor s judgment of a patient who has been bleeding as to whether shock is present or imminent If it is withhold morphine if it is not morphine may be used with advantage

Dr Cliffton Yes that is correct

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marked rise in portal pressure and enlargement of the liver an observation which led to the theory that the action of digitalis in humans is also due primarily to constriction of the hepatic veins with blockage of the blood in the liver Subsequent observations showed that there is something peculiar about the structure of the hepatic veins of the dog which applies neither to the cat nor to man and that in these species neither of these two effects occur

Dr Ephraim Shorr The phenomenon Dr Lee described occurs in the rat also The cat and the dog may not be as different as they seem for the sphincter activity which is concentrated in the hepatic vein may be represented by multiple sphincters in the smaller veins in other animals Both may therefore possess similar venous constrictor mechanisms

Dr Gold You are quite right Dr Shorr and there is the possibility that the cat may show the same kind of reaction to morphine in the shock state as the dog It would enhance the belief in the general applicability of the phenomenon however if it were actually demonstrated that it occurs in the cat

Dr Lee May I try to answer that?

Dr Reader Yes

Dr Lee We thought the dog would be a more appropriate animal for investigating the responses to morphine The dog is quantitatively more resistant than man but the effect of morphine on the central nervous system of the dog is qualitatively like that of man and unlike that of the cat Morphine depresses the dog and causes similar depression in man It excites the cat

Dr Gold These similarities and differences in species behavior to morphine can prove misleading There are conditions under which morphine causes the cat to fall asleep On the other hand while small doses of morphine cause somnolence in the dog large doses cause excitement and massive doses convulsions so that in the end the dog sometimes has the appearance of having received a toxic dose of strychnine I do not believe that we get very far with theoreti

Dr Solomon Garb It is my impression that in the case of battle casualties in the forward areas, aide men rather than physicians pursue the practice of giving all or most wounded men an injection of morphine In view of what has been said today, is that a justifiable idea?

Dr Reader I don't believe it has ever been a basic policy to give all wounded men morphine The idea seems to have developed among the corps men themselves Being armed with syrets, they believed they were expected to do something and the thing to do was to use the syret In my own contacts with corps men I found it easy to dissuade them from using it A blanket rule regarding morphine is a dangerous one, for many wounded men are not in pain also there are many in pain who are not necessarily in hemorrhagic shock or in danger of it

Dr Cliffton I would like to ask Dr Lee whether there have been any experiments carried out on human patients similar to those described in dogs You referred to one patient who went into shock and died fairly soon after a dose of morphine I wonder if that could have been a chance occurrence I have seen similar things happen in patients who have not had morphine You make rounds 10 hours after the operation, and while you walk past them, someone suddenly goes into collapse and dies without having had any morphine It seems to me that we should have more evidence before we say that the phenomenon in dogs holds in man

Dr Lee You are quite right The two cases I described are highly suggestive by reason of their analogous behavior but are not proof of this strange reaction to morphine which is firmly established in the dog

Dr Gold I would like to extend Dr Cliffton's comment and ask whether this phenomenon applies to the cat The dog is a peculiar animal The heart and the circulation of the dog are in some respects quite unlike those of the human and there are some inferences from the behavior of the circulation of the dog which may prove misleading when applied to the human I have in mind particularly the work on digitalis in which it was found that digitalis causes a

sufficient discrimination in the matter of the patient's weight and age and physical status

Dr McKeen Cattell It has been stated that a person in shock is peculiarly sensitive to anesthetic agents because they disturb his physiologic adjustments to the low pressure I would like to present the point that there are no adjustments available after shock develops When the blood pressure begins to fall, a maximum degree of vasoconstriction has already taken place, and under these circumstances any procedure applied to the animal may readily give rise to a further fall in the pressure This problem was studied during World War I In the normal animal a large amount of ether suddenly applied causes a fall in the blood pressure, and compensatory mechanisms come into play, so that as the anesthesia deepens the pressure actually rises It is otherwise in shocked animals In them the blood pressure fall at the beginning does not show a secondary rise, but continues on down and remains low during the anesthesia This has been shown not only in dogs but in cats

Dr Walter Modell Is it possible that the results which Dr Lee described might be due to the sum of two doses of morphine rather than to just the dose after the shock state?

Dr Lee No I believe not More than half of the dogs used in these experiments actually received the narcotic only after the shock experience, and none before

Dr Gold About 20 years ago we published a study from our laboratory, called *The Effect of Hemorrhage on the Susceptibility to Drugs* We bled cats 50 per cent of their estimated blood volume and tested their tolerance to various drugs including depressants, stimulants, and digitalis materials The results showed that the animals became very much more susceptible, the fatal doses declining to something of the order of one half that required by the normal animal Does that have any bearing on this problem?

Dr Lee It may be the same thing!

Dr Gold We thought at the time that it might have been due to a redistribution of blood with relatively larger amounts in the vital areas

Dr Shorr I think it is well that the concentration of our

cal considerations in defending the choice of the dog for these circulatory experiments Since the vascular organiza tion of the dog is known to be somewhat different from that of the cat, a difference which has proved misleading in regard to the study of the mechanism of digitalis action it seems to me desirable to test out in the cat the phenomenon of the special reaction to morphine in shock

Dr Cliffton I wonder whether Dr Lee would answer this question for my own information You have stated that it requires more morphine in the dog than in man to affect the central nervous system, can you be certain that the same holds for the vascular system? This would be important since these are vascular reactions you are concerned with in the particular shock response

Dr Lee No we do not have an answer to your question I might mention the fact that the original observation on the effect of morphine in the shocked animal was fortuitous We used to do the operation on the dog under procaine anesthesia, and when the animal got up it was apt to be somewhat excited Following the observation on the vessels we would give them 2 mg of morphine per kg intra venously We were intrigued by the observation that this dose caused only a transient fall in the pressure with slight arterial dilatation or no appreciable effect at all at one time and that then, in sharp contrast, the same dose caused ex treme and widespread dilatation when the dog had been previously in shock

Dr Artusio Although the crucial experiment has never been made in man to establish the phenomenon that has been described here there are numerous observations which indicate that it is to be found in man No one has deliberately tried to give large doses of morphine to

impairs vasomotor responses to a degree which may be su cient to lead to a blackout on the tilt table There is also the fairly common observation on surgical pavilions of post operative patients developing profound states of hypotension during attempts to treat pain when morphine is used without

type of shock Such patients in severe pain improve with the use of morphine Of course, the results are otherwise, as Dr. Artusio pointed out, when a patient who is out on the field in extreme cold, after a severe trauma, receives 2 or 3 doses of morphine, and then is brought into the warmth and begins to absorb the drug quickly Those are conditions that give rise to the shock reaction

Dr Shorr I should like to see some other term reserved for dubious states of shock, perhaps the term shock like states The term shock should be reserved for a state of persistent deficiency of flow In terms of the peripheral vascular phenomena, research in animals discloses no discernible difference between the shock caused by fatal hemorrhage or severe trauma

Dr. Reader Our time is up

SUMMARY

Dr Gold Circulatory shock is one of the common hazards and causes of disaster in the course of hemorrhage, trauma, and surgical operations, often occurring under conditions which permit of no decision as to the immediate factors which bring it about so often leaving one uncertain as to how one might do the thing differently next time The conference this afternoon revolved around a factor which was found, in animal experiments to predispose to irreversible shock, and clinical observations were presented which point strongly to the probability that the same mechanism operates in humans We have here then at least one factor which frequently enters into the situation of a patient in shock, which it is now possible to control Morphine and other narcotics, and general anesthetics, tend to interfere with the circulatory adaptive mechanisms and thereby tend to promote shock Morphine is a strong offender, Demerol less so The deleterious effect of a general anesthetic differs with the different anesthetic agents and with the depth of the anesthesia A dose of morphine which causes little or no circulatory effect in a particular person may, during severe hemor-

well to try it and see whether it prevents the hypotension without interfering with the analgesic properties of the narcotic.

Dr. Reader: It definitely does interfere with the analgesic properties of morphine. When given to addicts, it removes all the manifestations of morphine very rapidly.

Dr. Lee: Then I wonder if it would be of any value?

Dr. Gold: Might it not be of value in preventing a fatality in the case of one who has received by oversight or otherwise a dose of morphine in a shock state, such as the case of the woman that you cited earlier?

Dr. Lee: Yes, that is possible. Pitressin together with transfusion given early enough also reverse it.

Dr. Reader: Does Demerol come into the same class in connection with this question of narcotics in shock?

Dr. Artusio: Demerol is a lesser offender than morphine, but in these cases it has to be handled with much the same care. Demerol is not the answer to the problem.

Dr. Cliffton: I would like to ask Dr. Artusio another question as a matter of practical interest. He states that the particular sensitivity to shock develops only in deep anesthesia and that the difference between one and another anesthetic agent is not appreciable in light anesthesia. Since relaxation is so important during operations, does the use of some of the relaxing drugs like curare perhaps have the effect of rendering the patient susceptible to this shock reaction?

Dr. Artusio: Some of the muscle-relaxing agents in large doses possess ganglionic blocking actions which may not be advantageous, but some of the newer ones like succinylcholine when given with light planes of anesthesia have left the cardiovascular mechanism intact even during prolonged surgery in severe-risk patients.

Visitor: I believe that Dr. Cliffton distinguishes between hemorrhagic shock and other forms of shock in his use of morphine. Is there any basis for such a distinction?

Dr. Cliffton: I think there may be a distinction. Severe pain, for instance, occasionally produces a condition of shock which seems to me quite different from the hemorrhage

The Choice of Therapy in Intestinal Parasitic Disease

Dr George G Reader The choice of therapy in intestinal parasitic diseases is the subject of today s conference The discussion will be opened by Dr Kean

Dr B H Kean We might modify the title a bit by saying that we will discuss only the more common intestinal parasitic diseases There are a great many intestinal parasites but if we exclude about ten of the more exotic varieties, limiting ourselves only to those which we might encounter in the New York City area, we wind up with about 15 diseases These include amebiasis two flagellate diarrheas, five helminthic infections four tapeworm diseases, and schistosomiasis which is caused by a fluke This still seems like an ambitious undertaking for one session, and we shall try to deal only with as many as time will permit

I should like to say at the outset that much that is written about the results of various treatments should be regarded with suspicion It seems to be unusual to find an initial evaluation presenting the facts For example for many years we believed we knew how to treat ascariasis We used to speak of cures in about 90 per cent of the cases and that is what one finds in almost any textbook At the last meeting of the American Society of Tropical Medicine, 8 different persons from various parts of the world agreed that we are far from knowing how to treat *Ascaris lumbricoides,* and that currently the cure rate is only about 35 per cent

The situation in the case of pinworm is well known for there is no ideal therapy for this disease We shall discuss pinworm in more detail later

rhage, render the circulatory depression irreversible. A noteworthy feature of the phenomenon is that it persists for some time as a state of hypersusceptibility to shock even after the conventional signs have disappeared or have been abolished by transfusion, namely, the return of the blood pressure and the heart rate to normal. Much stress was placed in this conference on the wisdom of withholding morphine from patients in shock and of using morphine with much caution in those in whom severe hemorrhage is a possibility and in those who are just emerging from a state of shock The discussions dealt in much detail with the underlying mechanisms of the shock reaction during narcotics and anesthetics and with methods for treating it.

in dilutions which may reasonably be expected to prevail with therapeutic doses. It is, of course, easy enough to set up test tube culture experiments and demonstrate amebicidal actions with Terramycin or other drugs, but so far as we know, none of these, with the sole exception of emetine, kills amebae in therapeutically relevant dilutions. Emetine is potent against the amebae in dilutions of 1:5,000,000, and it kills amebae in dilutions of 1:1,000,000. There is, of course, the difficulty that emetine is a fairly toxic material. Strangely enough, in spite of its high amebicidal action, emetine alone almost never cures intestinal amebiasis. I don't have an adequate explanation for this phenomenon. Used in conjunction with certain other preparations, emetine is, of course, extremely effective in bringing about a cure.

Among the more popular members of the arsenical group, namely, Carbarsone, Balarsen, and Milibis, there is very little to choose. We prefer Carbarsone. There has been a great deal of experience with it over the years, and its toxicity is reasonably low for an arsenical compound. Some of you may remember the report by Anderson about two years ago in which he described the use of thioarsenites for amebiasis. This material has been found to be too toxic for clinical use and is not commercially available.

There is relatively little to choose among the preparations of halogenated hydroxyquinolines. We prefer Diodoquin. It seems to be the most popular among this group of materials. For many years it was the drug of choice in New Orleans where it cured about 95 per cent of cases of amebiasis. This cheery report was followed by other reports from England which declared the drug to be almost worthless. The United States Navy refused to include Diodoquin in its list of necessary drugs, mainly on the basis of the British experience. In recent years experience in New Orleans seems also to show a falling off of the cure rate. At the present time it is probably closer to 50 per cent, although most of the reports still refer to from 60 to 80 per cent.

Since none of these drugs is entirely satisfactory, we pursue

Let us for a moment consider the *most important* of this group of diseases, that caused by *Endamoeba histolytica*, or intestinal amebiasis Even if we leave out of consideration the archaic drugs which clutter up the field and consider only those currently in use, the list is large emetine, various arsenicals like Carbarsone, Milibis, and Balarsen, the halogenated h[illegible]

and

do not come to mind at this moment Five or six years ago when bacitracin became available it appeared that the cure of amebiasis had been found That illusion lasted only a year, for the cure rate dropped to about 20 per cent Aureomycin was the next drug to appear with initial cure rate approximating 95 per cent These rates have now dropped to about 30 to 50 per cent The initial reports in the case of terramycin were very optimistic There was one report that 60 people were treated with Terramycin, 2 Gm a day for about 10 days, that the cure rate was 100 per cent and that there were no toxic symptoms, no diarrhea no nausea no complaints It is my experience that you cannot give 2 Gm of terramycin a day to 60 patients without receiving complaints Terramycin is still being used and is probably the best single drug for amebiasis, but the ultimate evaluation of its efficiency requires an open mind Fumagillin is another of the special cures for amebiasis By the time the drug appeared on the market, the cure rate was dropping from 90 per cent down to 75 per cent One can predict that in a year or so the cure rate will be still lower It should be noted that terramycin affects bacteria to a much greater extent than does fumagillin Tetracycline is being evaluated at the present time Chloroquine diphosphate might also be mentioned it is virtually useless for intestinal amebiasis but very important for the treatment of hepatic amebiasis in conjunction with emetine

Emetine is, of course used for both the intestinal and hepatic forms of amebiasis There is something strange about this drug It is the only one among all of the drugs previously mentioned that is a true amebicide, that is it kills amebae

who believes that he is perfectly well and may even regret that he has had the misfortune of having had his stool examined as the result of which a parasite is found The plan of therapy which I outlined might be accepted readily as appropriate for acute amebic dysentery when it is necessary to alleviate the patient s symptoms But there may be a doubt as to whether one is justified in using this heroic treatment in a person who seems perfectly well Experience indicates that many people with so-called asymptomatic amebiasis who think they are perfectly well are not really in perfect health but are able to recognize this fact only when the so called asymptomatic disease is cured It is very much like a patient with a low grade of anemia who does not know how well he can be until the anemia is cured All patients with amebiasis should be treated There is still some question as to whether the treatment should be as thorough in these cases as in the symptomatic ones It is our inclination to treat them in the same way We warn the patient that he may feel worse during the treatment but that he may anticipate feeling better when it is over than he did before the therapy was started

Dr Reader We might ask if there are any questions about amebiasis before we go on to some of the other parasites Dr Almy do you have any comment on the treatment of amebiasis?

Dr Thomas P Almy I was wondering about the feasibility of giving 5 daily injections of emetine to ambulatory patients who do not have any symptoms that they will admit to Are you not forced at times to modify the schedule, and if so just how do you do that?

Dr Kean You have called attention to a most important point It is especially applicable to treatment of large numbers of patients in clinics There we are inclined to eliminate emetine from the program and carry out only the other parts of the schedule The pain of an injection of emetine is sometimes considerable One cannot use a drug with the potential toxicity of emetine in hundreds of individuals in clinic populations without occasionally getting into some difficulty

the plan of using several drugs, stretching the treatment over long periods of time Here is one plan we use in the treatment of amebiasis We give a grain of emetine (65 mg) intramuscularly daily for 5 days It may be mentioned parenthetically that, in the case of the 5 day therapy, electrocardiographic control is not necessary It is desirable to use electrocardiographic checks when the treatment is carried on over a longer period of time, say 10 days, as in the case of hepatic amebiasis or in older persons With a shorter period of treatment, some changes in the T waves may appear, but they are unimportant from the practical standpoint and if there has been no untoward reaction to the first dose of emetine, it is unlikely that anything serious will occur during the first 5 days This is not true, however, in the case of a longer treatment Simultaneously with the emetine we start Carbarsone, 1 Gm daily, and it is continued for 10 days one 0 25 Gm tablet being given 4 times daily This is then followed by a course of Terramycin, 1 5 Gm the first day and 1 Gm daily thereafter for a week If the patient seems to be able to tolerate a little more terramycin it may be given for 10 days This schedule constitutes our initial effort to cure a patient of amebiasis We expect a cure in about 90 per cent of the cases by this method If a follow up reveals that the parasite has returned, the whole course of treatment is repeated, adding in addition a 15 or 20 day course of Diodoquin We usually give 2 5 Gm daily in divided doses to an adult This should result in the cure of a fair number of the 10 per cent failures There is still a small residual group which is resistant to cure and which constitutes quite a problem

Dr Harry Gold Would your general formula of treatment apply to the asymptomatic form of amebiasis as well?

Dr Kean There have been some question and considerable debate about that over the years Now with the known danger of hepatic amebiasis, and with the fuller recognition of the importance of the public health aspects of the disease the debate is almost over Consider for a moment what one means by a case of asymptomatic amebiasis This is a patient

the cyst passes the stomach unharmed and in the intestine divides yielding trophozoites These trophozoites invade the mucosa destroy portions of the submucosa and lead to the impairment of the blood supply with eventual ulceration of the mucous membrane The question that has come up is this Is the conversion from trophozoite to cyst a reversible process in the same patient? A certain number of tropho zoites instead of invading tissue round up and form cysts which may be passed in the stool Can these newly formed cysts divide and release trophozoites without crossing the gastric barrier of a new host? There is no final answer

Dr Reader I wonder if Dr Grace would care to express an opinion as to why some people develop acute dysentery from the ameba and others carry the organism without de veloping the disease? Do you believe there is something in the nature of bowel function which determines the course?

Dr William J Grace There are some observations that indicate a relationship between the character of the intestinal tract and the susceptibility to symptoms in amebiasis We have had a few *patients who developed symptoms of amebi* asis only during periods of stress It seems to be a fact that the condition of the mucosa of the gastrointestinal tract determines the ability of organisms to penetrate Norris and Rappaport made some experiments along that line They gave an irritant enema of turpentine Under ordinary circum stances 10 per cent of the animals could be infected whereas under these unusual conditions the infection rate went up to 50 per cent The observations that we have on changes in the mucous membrane under the reaction of stress indicate that the membrane becomes more fragile and that some alteration in mucous formation takes place It is my notion that this is the kind of condition most likely to lead to in fection by an organism which otherwise might prove in nocuous

Dr Reader Do you have any opinions on this point Dr Kean?

Dr Kean Attempts have been made to increase the rate of infectivity in experimental work by irritating the intestinal

We are less apt to encounter this trouble in the case of the more individualized care of private patients and in such cases we are apt to carry through the full regimen of treatment I would be interested in knowing what you think about this Dr Almy Do you prefer to use one drug at a time and see how the patients get on and if they are not cured then to turn to another drug or do you prefer to use several measures at the same time?

Dr Almy I have been using only one drug but I am perfectly happy to use two or three I would be very much interested in a convincing demonstration of the differences in the results

Dr Reader Dr LeMaistre, I wonder whether you would have any idea as to why Terramycin is so effective and Aureomycin not?

Dr Charles A LeMaistre I am inclined to think that the difference between the two is accentuated by studies and data that are not of equal quality On reviewing the data on aureomycin a few months ago I was impressed with the fact that the evaluation of this drug has not been as careful extensive, and thorough as it has been in the case of Terramycin It may well turn out that the two are not materially different but at the present time, as Dr Kean knows I personally prefer Terramycin

Dr Almy I was rather cast down to hear Dr Kean imply that an ancient explanation is probably not correct It used to be said that emetine is ineffective against the cyst form of the ameba and since the cyst form could not be eradicated from the lumen of the intestine it reinvaded the bowel and in that way prevented a cure Is that now thought to be incorrect?

Dr Kean One cannot be certain whether it is or not You all remember that amebiasis is usually acquired by drinking contaminated water If in this way, the trophozoite is ingested no harm is done because it does not survive the gastric barrier even though this is the form of the ameba that is so dangerous to the host On the other hand the ingestion of the cyst form gives rise to the disease because

Dr Kean We believe the evidence is fairly strong that the only hepatic lesion in amebiasis is a localized abscess, and that amebiasis does not cause a specific diffuse hepatitis This view is held despite the numerous articles to the contrary Any enlargement or tenderness of the liver, or changes in the liver function tests, which are thought by some to be caused by diffuse amebic hepatitis, are manifestations of nonspecific changes in liver seen in any ulceration of the intestinal tract For the treatment of amebic abscess, there are two effective drugs—one is emetine, and the other is chloroquine diphosphate Emetine has been the standard drug for many years A course of treatment is 10 daily intramuscular injections of 1 grain or 60 mg each After a rest period of 3 or 4 weeks, the course of treatment may be repeated In the past 5 years or possibly a little longer, Conan has been using chloroquine diphosphate Its use is based on knowledge derived from studies of malaria, where it was shown that chloroquine was concentrated in the liver It seems to be just as effective as emetine The dosage schedule has not been completely worked out It appears that 1 Gm the first day and 0 5 Gm daily for the next 2 weeks is a reasonably satisfactory program It is a cumulative drug, but its toxicity is not high At the present time we do not yet have the courage to depend upon this drug alone, and so we use emetine and chloroquine in alternating courses Dr Conan has had very good results using the chloroquine alone

Dr Gold Has Terramycin any value in amebic abscess?

Dr Kean Yes and no Terramycin sometimes brings about a spectacular drop in the temperature and in the signs of intoxication, the chills and general malaise Approximately one third of the patients with amebic abscess develop a secondary infection, and the invaders are usually the colon bacilli Terramycin produces its spectacular effect by acting on these, but it will not destroy the amebae, and hence this striking change in the picture is only a temporary one There is no objection to using Terramycin in conjunction with emetine and chloroquine

tract with croton oil, and there is some evidence that the rate of infectivity may be increased in this way You might be interested in the relationship between mucous colitis and amebic dysentery This is not directly an answer to Dr Reader's question but is related to it in that it has to do with the state of the mucous membrane and its susceptibility to infection The matter stems from some army experience There are a number of individuals in the Veterans Hospitals or drawing disability pay who have a diagnosis of amebiasis but who actually have ulcerative colitis What happened in the past was this The patient came in with symptoms of colitis Amebae were found, and the patient was thoroughly treated Later he had a recurrence The recurrence was called amebiasis He was again treated, and later he had another recurrence The last episode, which was called a recurrence, was no longer, however, amebiasis but ulcerative colitis Now the stool no longer showed parasites Does this mean that amebiasis produced the picture of ulcerative colitis? Does this indicate that the patient had a potential susceptibility to ulcerative colitis and that an appropriate trigger brought it out, in this case the attack of amebiasis? There are those who believe that in ulcerative colitis bacillary dysentery is the trigger One must, of course consider the fact that if 10 per cent of the population has amebiasis, there are a certain number of cases in which the two diseases overlap

Dr Grace We have seen a few cases in our *clinic* of the kind that Dr Kean has described, namely, individuals who showed all the characteristics of an ulcerative colitis and in whom the ameba was found in *the stool It was my* feeling that the ameba was just an incidental finding

Visitor I don t think you said very much about the hepatic abscess *You did mention 10 days of emetine* in the case of hepatic abscess Could we hear more about this?

Dr Kean The reason I did not go into it is that the subject *of this conference is the treatment* of intestinal parasites I could go into it if you like

Dr Gold Go ahead

Dr Kean We believe the evidence is fairly strong that the only hepatic lesion in amebiasis is a localized abscess, and that amebiasis does not cause a specific diffuse hepatitis This view is held despite the numerous articles to the contrary Any enlargement or tenderness of the liver, or changes in the liver function tests, which are thought by some to be caused by diffuse amebic hepatitis, are manifestations of nonspecific changes in liver seen in any ulceration of the intestinal tract For the treatment of amebic abscess, there are two effective drugs—one is emetine, and the other is chloroquine diphosphate Emetine has been the standard drug for many years A course of treatment is 10 daily intramuscular injections of 1 grain or 60 mg each After a rest period of 3 or 4 weeks, the course of treatment may be repeated In the past 5 years or possibly a little longer, Conan has been using chloroquine diphosphate Its use is based on knowledge derived from studies of malaria, where it was shown that chloroquine was concentrated in the liver It seems to be just as effective as emetine The dosage schedule has not been completely worked out It appears that 1 Gm the first day and 0 5 Gm daily for the next 2 weeks is a reasonably satisfactory program It is a cumulative drug, but its toxicity is not high At the present time we do not yet have the courage to depend upon this drug alone, and so we use emetine and chloroquine in alternating courses Dr Conan has had very good results using the chloroquine alone

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Dr Reader Perhaps we should go on to the next group Would you say a word about the flagellates, Dr Kean?

Dr Kean I think we can dispose of these very quickly *Giardia lamblia* has a standard therapy that is effective There is no alternative The drug is one which was used in malaria quinacrine hydrochloride or Atabrine In the usual schedule one gives 5 tablets of 0 1 Gm each the first day, that is 0 5 Gm, and then 3 tablets, or 0 3 Gm, in divided doses daily for a week or 10 days The cure rate is about 90 per cent After a week or 10 days one can repeat the course There is some debate on the question as to whether *Giardia lamblia* causes disease There is fairly good evidence, however, that about half of the individuals who have this parasite are subject to bouts of diarrhea, symptoms of dyspepsia atypical gallbladder disease, peptic ulcer, or so called gastric neurosis I shall not forget the aged dowager who developed severe colitis late in life It was felt that she had a malignancy She was ill for about 6 or 8 months She would not go to the hospital and would not allow herself to be thoroughly examined It was finally decided to try to do a barium enema in her home All the equipment was brought there and two very competent radiologists made the examination No malignancy could be demonstrated at that time About 6 more months elapsed without results, when someone thought it might be a good idea to examine the stool *Giardia lamblia* were found in great numbers On the third day of quinacrine therapy the disease was brought under control This is an exaggerated case, but it helps to point up something that is worth stressing It is disturbing to contemplate how extensive a medical work up will be done before a stool examination is made Fortunately that is not so in this institution

We might now go on to the subject of tapeworms I like to talk about this because there has been some advance in treatment of these worms in the last few years The classical drug in the treatment of tapeworm is oleoresin of aspidium It was used by Theophrastus in 300 B C and it has been a very effective agent against the tapeworm However it has a fairly high order of toxicity and has been largely replaced

by quinacrine hydrochloride (Atabrine) as the drug of choice. In view of the effectiveness of quinacrine and its much lower toxicity, as well as its applicability to all the common types of tapeworm, it would in these days be difficult to defend the use of the older remedy of oleoresin of aspidium.

The mode of administration of these drugs is a decisive factor. The parasite is attached by a tiny, hardly visible head to the mucous membrane of the duodenum. The problem is to get a high enough concentration of the drug to act at the site to which this head is attached. Neither of these drugs actually kills the parasite. They so affect the nervous system of the parasite that the head releases its hold on the mucous membrane. Thus the entire parasite with its head moves past the duodenum into the small intestine and beyond into the large bowel where it no longer can take hold. The medication should be administered at a time when the intestinal tract is as empty as possible. The patient is instructed to have anything he wants except alcohol up until noon. If possible it is best to skip the dinner or supper. If he then takes a saline carthartic that night, we may presume that the intestinal tract, or at least the upper portion of it, is reasonably empty by morning. The medication is given in the morning instead of breakfast. There are those who give quinacrine in tablet form by mouth. The patient swallows a tablet every 2 minutes until all 10 have been taken, making a dose of 1 Gm. The drug is quite irritating to the gastric mucosa and frequently a good portion of the dose is regurgitated. The cure rate by this method is only about 70 per cent.

We prefer the method of transduodenal intubation for administering the medication. A duodenal tube is passed. It is possible to control its position by means of the fluoroscope, but that is not necessary. If the tube is down to a level where a little bile can be aspirated, we can assume we are in the appropriate region, although it may not be actually in the duodenum. The quinacrine is then introduced into the tube. Two hours later the patient receives another dose of magnesium or sodium sulfate. The batting average by this technic is quite high, the cure rate being about 90 per cent. On a

eggs and then introduces the eggs into the mouth, thus completing the cycle. There has been a good deal of discussion about the wide distribution of the pinworm eggs They have been found in strange places, on chandeliers and under carpets, but if those locations were of any *importance*, we would probably all have pinworm disease. The factor that keeps the disease going is the scratching of the anus and the subsequent introduction of the eggs into the mouth Anus scratching is a very common practice. It is done by about one-third of children and by many adults. If you were to paint the perianal region with methylene blue, you would be surprised to see how often dye would be present on the fingers in the morning. Or dip the fingers in the morning in a culture medium, and see how often colon bacilli will grow out.

In order properly to evaluate a therapeutic agent in the treatment of pinworm, it is necessary to ascertain first what can be accomplished by the measure of stopping the child from scratching at night. If this measure were successful, the cure rate for pinworm would approximate 100 per cent The adult female of the pinworm lives only 8 weeks, hence, if reinfection can be prevented, the disease will be cured in 8 weeks. It is difficult to determine the value of drugs in pinworm because studies fail to distinguish the role of drugs and hygienic measures. Both have usually been employed together.

Hygienic measures are the most important part of any regimen of treatment. The first thing to do is to try to control the itching An antipruritic ointment of one kind or another is applied For a long time the ointment of ammoniated mercury was used We happen to prefer a preparation called Perazil ointment which contains an antihistaminic and a surface anesthetic. There must be a great many others that are just as good We have made use of the seal in type of pajama, a one-piece garment in which a zipper goes up to the top It can be tied at night The rear is so sealed that the child must take off the garment in order to use the facilities. A pair of underpants is worn underneath the one [illegible] No [illegible] child can at[illegible] scratch at[illegible]

as he wants The urge to scratch the anus is irresistible Dr Hall photographed children with pinworm disease after having them tied up so as to try to prevent scratching He found that when the hand could not be brought to the anus, the anus was brought to the hand by a process of bodily contortion which was almost unbelievable

If, then the child is sealed in by this method and an ointment is used to allay the itching, the outlook for cure of pinworm disease is I would say, about 50 per cent This figure applies to adults as well I believe that a great many of us have had pinworm disease and have cured ourselves simply by hygienic measures, by washing the hands after anal scratching

Now, how about the use of drugs? As I have already stated, there are a great many drugs that have been employed Hexylresorcinol is quite effective, but its toxicity is too high for use in a disease so benign Terramycin, gentian violet, and piperazine citrate are the drugs of choice at the present time The pinworm is a parasite too tough to kill Terramycin simply deforms the eggs so that a certain percentage lose their viability We don t know quite how piperazine citrate acts Gentian violet appears to have some effect on the adult worm as well as on the eggs What we aim to do is to establish a cycle of biological attrition in which more of the parasites die off than are acquired over a particular period of time That seems to be the best that can be done As in the case of other parasites, so in pinworm disease the cure rates vary considerably Dr Harold Brown at Columbia obtained cure rates as high as 85 per cent with piperazine citrate Our own results with this compound are only about 50 per cent It is easy to understand the higher cure rates in a well planned experiment in which all the details of treatment can be checked and controlled The cure rate falls off considerably when the drug is used under the more usual clinical conditions Our practice is to use all 3 drugs Terramycin for 3 days gentian violet for 7 to 10 days and piperazine for 7 to 10 days We have stopped using diphenan

Dr Gold I wonder what the results would be if one of

envisage more than the choice of a remedy. The most efficacious therapy is not necessarily the one suitable for adoption in a particular area or instance. Considerations include toxicity, ease of administration, cost and length of medication, and the patient's ability to cooperate in a therapeutic regime. One can hardly expect to cover the entire field in one session. Dr. Kean wisely selected for discussion a few of the diseases commonly encountered in the New York City area. However, these are not peculiar to this city but are widely prevalent throughout the world, and this fact has added wider significance to the discussion. This session has been profitable in developing the perspective necessary to an appreciation of the general problems of treatment of parasitic infections of the intestine.

A long list of drugs is available for therapy in intestinal infections, some old, some new. The point was made that reported results of various treatments should be regarded with suspicion, inasmuch as initial evaluation seldom presents the facts. In intestinal amebiasis, because of unsatisfactory results with individual drugs, the treatment plan discussed includes a combination such as emetine, an antibiotic and an arsenical; additionally, in cases of recurrence, a halogenated hydroxyquinone derivative. Details regarding choice of drugs, dosage, length of medication, and related problems were outlined and discussed. There was considerable discussion regarding the course to be adopted in cases of asymptomatic amebiasis. The consensus of the conference was that in view of the public health aspects of the problem and the potential danger of hepatitis, such patients should be treated, wherever practicable, using the same plan suggested for acute amebic dysentery. It was pointed out that these patients, who thought they were in good health, felt much better after a course of therapy. Other items of interest included the comparative efficacy of Aureomycin and Terramycin, the role of stress in precipitating attacks of amebic infection by inducing changes in intestinal mucosa, and the relationship, if any, between amebiasis and ulcerative colitis, as well as the question of whether cysts formed in the intestine of a host

can divide and release trophozoites without crossing the gastric barrier of a new host In hepatic amebiasis, the lesion is a localized abscess and not a diffuse hepatitis Recently chloroquine has shown promising results, but perhaps it is not yet safe to use it to the exclusion of emetine The effect of Terramycin, which is sometimes spectacular, is related to eradication of associated bacterial infections, not to any specific action on amebae

Atabrine, now rarely used as an antimalarial, has recently found two useful applications in the treatment of infections caused by *Giardia lamblia* and tapeworm In the former, it is the standard drug In the latter, it is at present preferred to the classical remedy, oleoresin of aspidium The problem in tapeworm infections is to get a high concentration of the drug to act at the site to which the head of the worm is attached The mode of administration in this disease is therefore a decisive factor Details of preparation of the patient, administration of medication, and evaluation of the results were fully discussed In pinworm infection, the importance of hygienic measures has been emphasized Since the life of the female worm is about 8 weeks, prevention of reinfection for this period could eradicate the disease by hygienic measures alone *However, it is current practice to combine* hygienic measures with drugs It is noteworthy that enemas, a time-honored favorite, are considered ineffective no matter which drugs may be employed

Utility of Medications in the Treatment of Headache

Dr George G Reader The place of drug therapy in the treatment of headaches and the selection of an appropriate agent constitute the subject of the conference this afternoon Dr Harold Wolff will open the discussion

Dr Harold G Wolff As you well know, headache is probably the commonest complaint with which the physician must deal, and fortunately about 95 per cent of all headaches are benign as regards significance Thus, less than five per cent call for heroic and life-saving measures There is no way of telling from the intensity of the pain or its localization whether the significance is benign or ominous There are a great many features which help us in diagnosis but it is not the purpose of this discussion to focus upon them We are going to consider the management of headache in terms of drug therapy, and I would like therefore to consider the headaches that are not due to tumors abscesses, hematomata, meningitis, or ominous disease of the nose and throat As I said, this large group comprises about 95 per cent of all headaches and this constitutes a good part of medical practice

There are three mechanisms involved in common headache vascular structures on the outside of the head are most frequently involved a second type also occurs frequently and is perhaps almost always linked with the first headache due to sustained contraction of the muscles of the scalp and neck, and thirdly, linked with the first two and of a variable and uncertain frequency, there are those headaches that have to do with swellings and disturbances of

the mucous membranes of the upper airways, especially the nose and paranasal spaces

Let us begin with consideration of vascular headaches, probably the most common type of the more or less completely reversible disturbances, reversible in the sense that the disorders responsible for them or the tissue changes which give rise to them are completely reversible These vascular headaches can be of any duration, any intensity, in any part of the head, can occur any time of the day or year They have innumerable names depending on where they occur and under what circumstances, and can be so mild as to call for no attention whatever, as is true in most individuals or be so severe as to challenge the therapeutic equipment of the physician Vascular headaches involve the blood vessels both small and large There are three phases of the headache the first is the vasoconstrictor phase, the second, the vasodilator phase and the third is the edema phase associated with other effects that I will mention A typical vascular headache attack, if there be such a thing, starts in with vasoconstrictor phenomena These may be exhibited as pallor of the face, and in about 10 per cent of attacks, by transient disturbance in vision, such as flashes of light and scotomata difficulty with speech, and defects in movement or sensation of the hand or arm Visual disturbances may come from constriction of vessels of the retina or of the cerebral cortex Other motor and sensory disturbances presumably come from vasoconstriction in the cortex These symptoms may persist for a few minutes from 5 to 45, usually Then the individual is free of any discomfort for a few minutes, after which the headache begins and may persist for half an hour to days, but usually from 4 to 12 hours It is common for the headache to begin in the morning and end at the close of day In the third phase of the attack certain individuals who have vascular headaches exhibit edema of the face, not preceding, but during and after the attack In some individuals there is a gain in weight, perhaps 8 10 pounds, before an attack, with a corresponding weight loss during and following it Sometimes hemorrhages

occur in the painful areas of the head, and on rare occasions well defined hematomata occur during this phase The spinal fluid may occasionally be discolored during the headache attack Visual disturbances may be associated with this painful phase of the attack They are not the transient loss of vision, flashes of light, or scotoma of the preheadache phase but usually are manifested by difficulty in focusing and blurred vision, associated with changes in the size of the pupil and with defects in focusing The individual feels prostrated and looks tired and sick He may have vomited during the attack This is, in a few instances, the phase in which ophthalmoplegic migraine manifests itself by ptosis and impaired control of extraocular muscles, notably those supplied by the third cranial nerve In the rare individuals who have these symptoms they may last for a few days to 2 weeks and then clear up

A definition of the migraine type of vascular headache includes these phenomena the attack is ushered in by feelings of anorexia, nausea, and vomiting attacks are recurrent headache is usually one sided to begin with and may become generalized before the attack is over In a few instances as already mentioned, in perhaps about 10 per cent of those who have migraine, there are associated disturbances in visual or motor and sensory function, the painful phase of the attack is remarkably modified by vasoconstrictor agents The occurrence of migraine headache runs in families

Now, what therapy can be applied to each of these phases? The vasoconstrictor phase is often quite alarming Individuals who repeatedly suffer with vascular headaches may have one or two or half a dozen with visual, motor, or sensory prodromata These are apt to be followed by rather severe headaches but it is not always so Some individuals merely have repeated attacks of mild headache with visual disturbance The breathing of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen at such times is usually effective in terminating visual or sensory disturbances and occasionally preventing the subsequent headache The inhalation of amyl nitrite at such times interrupts the course

of the series of events just mentioned Usually no special treatment is given because the phase of vasoconstriction is so brief, and most people are not in a position to obtain the mixture of carbon dioxide and oxygen when needed

The headache attack itself is associated with vasodilatation There is a change in the tissues of the scalp in which the deep pain threshold is lowered at the time of the attack and for 6 to 8 hours, and possibly longer, after the headache per se has ended It is as though the tissue suddenly lowers its threshold, and pulsations that ordinarily do not hurt now begin to hurt We had suspected this factor for a long time, but it was not until the last year that the evidence for it was demonstrated in our laboratory Repeated observations on a series of subjects with headache revealed that lowered deep pain threshold about the extracranial arteries and adjacent tissues was an invariable accompaniment of the headache Those individuals subject to vascular headaches exhibited a heightened variability in the contractile state of specific portions of the cranial vascular tree, especially notable during periods of frequent attacks At such times after a period of conspicuous variability in contractile state of the cranial arteries there followed a phase of vasoconstriction succeeded by dilatation, intramural vascular edema, and lowered pain threshold Under the circumstances vasodilatation becomes painful, and the headache attack ensues The therapeutic aim at such times is to bring the vessels back to the premorbid state Very often a cup of hot, strong coffee will do it With less intense headaches—and many of these attacks are mild—a cold compress applied to the pain area, or the pressure of one's hand, or a tight bandage around the head will relieve the discomfort Familiar is the picture of the medical student preparing for finals with a bandage around his head and the coffee pot boiling at his elbow

Ergotamine tartrate is useful for the more severe headaches as an agent that specifically constricts blood vessels, more especially those around the head It exerts some side effects, notably nausea and vomiting in a few patients and

some transiently elevated blood pressure. Within half an hour or 45 minutes of the intramuscular injection of 0.5 mg. of ergotamine tartrate the vessels change their size, and the amplitude of their pulsation diminishes. The pulse wave which results from a study of the arteries changes its form to that of a constrictive phase. This, when accomplished, whether it takes 10 minutes, an hour, or an hour and a half, is usually associated with a reduction or a loss of the headache. This occurs in well over 90 per cent of the instances. Ergotamine tartrate taken by mouth is less effective, affording relief only about half of the time. Variations of ergotamine are advocated for one reason or another. These appear to be not strikingly more effective. One of these is DHE-45 which does not produce nausea and vomiting but is only about half as effective as ergotamine in eliminating headache. Combinations of caffeine and ergotamine are alleged to have advantages. They are often effective, but it is very hard to ascertain whether the combination is any better than ergotamine alone.

Aminophylline has been mentioned for headaches associated with hypertension. It has not been tried on a large or systematic scale, and I cannot be sure that it has any value. Its use is based on the thesis that aminophylline contracts intracranial vessels. Doubt about its usefulness in headache arises from the fact that it is not certain how much the intracranial vessels are involved in the headache of hypertension, since the vessels that are most commonly implicated are on the outside. This is a subject for further experiment.

ACTH has been tried in patients with migraine. It seems to be somewhat better than a placebo. It ends a headache in about 4 or 5 hours, whereas in the case of a placebo 8 to 12 hours elapse before the headache ends. ACTH improves the contractile state of the extracranial vessels. This is an interesting aspect of the properties of ACTH although not very important from the therapeutic standpoint. Norepinephrine, owing to its vasoconstrictor action, is effective in relieving a vascular headache attack in many individuals. It may be administered intravenously in a dilution of 4 cc.

of 0 2 per cent solution in a liter of 5 per cent dextrose in water at an average rate of 1 drop per second, or sufficient to raise systolic blood pressure 20 to 40 mm Hg In general, the more intense the headache, the longer the time required for its termination—i e, from 30 to 160 minutes The amount administered must be under control at all times

There are other constrictor agents that might be mentioned in the treatment of vascular headaches, but none of them is quite as effective as ergotamine tartrate or norepinephrine Then there is the group of analgesic agents which is represented by aspirin There are various combinations of aspirin with other members of the group, such as acetanilid or aminopyrine None of these has advantages over acetylsalicylic acid (aspirin) which is cheap and benign A dose of 0 6 Gm of acetylsalicylic acid is useful in headaches of mild to moderate severity. For more severe headaches, a dose of 60 mg of codeine is strikingly effective It is especially useful for those individuals who don't like to take hypodermic injections and who are made sick by ergotamine tartrate Codein in 60 mg amounts taken at night is usually sufficient to carry a person through and find him comfortable the next day When any of these agents are taken, it is well to interrupt the day's work Ergotamine tartrate should not be given more than once a week On the other hand, there are a few individuals on record who have taken this material intramuscularly in amounts of 0 25 to 0 5 mg several times a week for long periods of time, up to several years with few or no manifestations of intoxication The margin of safety with this agent is remarkable if the patient is free of hypertension, hepatitis, or heart disease

Morphine is occasionally used and may be given in a dose of 15 mg to an individual who is so disturbed so depressed, so frightened that in the judgment of the physician a good night's sleep appears to be imperative However, one does not embark upon this medication with enthusiasm since there is the possibility of repeated attacks and the dangers of addiction That about completes the story as regards the

use of drugs There is nothing new or more elaborate or better than any of these standard agents

Dr Reader Are there any questions?

Dr Harry Gold Dr Wolff, would you like to say whether you consider these agents as applicable to the isolated attack of headache or as a means for the long term management of these patients? Another question came up in my mind as you were speaking You described the physiologic mechanism by which the actual pain in the head may be produced What sets the mechanism into motion, what gets it going? What makes those very vessels constrict and dilate and in the course of so doing give rise to pain? Could we have your notions about that?

Dr Wolff All I have said this afternoon has to do with the attack itself Nothing that comes out of a bottle is of much help in postponing attacks or in preventing them Attacks come in individuals of certain equipment at the end of a sustained period of effort with fatigue and tension and sometimes when there is a sudden change of tempo from one of greater effort to one of less effort It is common enough to have the attack precipitated when there is any sudden demand made upon the individual who is already being strained considerably Either an extra load or a sudden reduction of the load calls for a new adjustment at a time when the individual is not up to it I see these headaches then, as an aspect of a life adjustment of which the major feature has to do with extraordinary application, doing things better than and longer than most individuals, out lasting others at the usual tasks In a sense it might be thought of as a depression syndrome since it comes at the end of, rather than in the setting of, the particular adaptation pattern operating Dr Tunis has been watching these people for several years and he observes them sometimes around the clock It is found that the blood vessels become unsteady They start to constrict, then dilate, then constrict, then dilate They behave in an uneasy way and finally, just before the attack begins, the uneasiness expresses itself in lively vaso constrictor action In a certain number of individuals the

attack may be interrupted by a physiological readjustment like standing upside down which calls forth a cranial vasoconstrictor effect. This is, of course, of no particular therapeutic helpfulness, but does suggest that neurogenic effects may interrupt an attack. The fact that an attack may be stopped by suggestion, hypnosis, enemas, or nonspecific medicaments also points to the operation of a neural factor. The placebo is a strikingly useful agent, not so much for the attack itself, although placebo injections of saline sometimes alter the mechanism, cause constriction of the dilated arteries, and end the attack. It is my guess about the attack that some central disturbance is ultimately converted into impulses causing a vasoconstrictor effect on one side of the head, followed by another barrage of efferent impulses causing dilatation. The lowering of the pain threshold, also the edema that is associated with the attack, probably cause the vasodilatation to be more painful. There is also a retention of potassium which perhaps heightens the vasomotor liability.

Dr. Gold: Have you deliberately avoided the use of the term "psychic" in relation to the cause of headaches?

Dr. Wolff: I prefer to say that the individual is reacting to stimuli in terms of his past experience and attitudes. I don't like the word "psychogenic" because it implies that the individual acts independently of the outside world of agents, events, and people.

Dr. Gold: It seems to me, then, that in the train of causation, the environmental experience serves as a trigger for a psychic mechanism lying in the unconscious mind, aroused by an experience in consciousness or by a particular thought, the conflictual charges expressing themselves in this vascular mischief. I know a physician who was subject to severe attacks of migraine during a period of 15 years and who took approximately 200 injections of Gynergen (ergotamine tartrate) a year, who then developed an attack of coronary thrombosis, and with this all attacks of migraine vanished, also the need for ergotamine. What made an attack of coronary thrombosis serve as a cure for his attacks of migraine? Whatever purpose the attacks of migraine were serv-

ing, this patient seemed to be equally satisfied by a new, serious, and disabling illness, the coronary thrombosis The question is what was this psychic need?

Dr Wolff We have one instance of a patient who had vascular headache of the migraine type of many years duration who developed general paresis This perfectionist individual, with the increasing damage of his brain, lost his headaches He is an example of how an imposed alteration in the relation of a man to his environment causes him to lose his headaches

Dr Gold Do not these very striking examples suggest the idea that many of the less distinctive types of headaches may also be called forth as well as relieved by psychic changes? I cannot escape the belief that underlying these headaches are bursts of impulses coming from unconscious psychic material of a conflictual nature aroused by life s situations which are often unpredictable and not often accurately pinpointed by the patient It may be an actual event or just a thought which serves as a trigger. That is why they come on at times in situations which puzzle the patient as well as the doctor The patient may say that he had been sitting quietly or reading a newspaper when the attack appeared and may have been totally unaware of what was going on in his mind at the time The therapeutic problem, as I see it is to get at the structure of this unconscious conflict for unless one is able to do that in one way or another, I am inclined to believe that one has very little to offer in the way of a cure

Dr Wolff I would subscribe to everything you have said except that I would include conscious as well as unconscious factors

Dr Gold I can understand that, if the conscious experience is taken to serve only as a trigger for a psychic charge which lies in the unconscious mind The reason one gets a severe headache from an experience which one recognizes in consciousness and can control is that it arouses a mechanism in the unconscious over which one has no control, and it

seems to me that in such a case one might deal with conscious causes or triggers indefinitely without effecting a cure

Dr Reader Is there any way of getting at these through drugs Dr Wolff or is it purely a matter of psychotherapy?

Dr Wolff Not through drugs Most of us manage our affairs alone We get into trouble and we get out of it and we make the same mistake several times during a life time Finally by trial and error, we work out some sort of adjustment If we understand the nature of the process in volved it is quite possible to make an adjustment by a little turning in on one s self appraising one s self in terms of where one is going what one is doing and what price one is willing to pay for goals This is the business of living In this the doctor can be of help I like to think of this as something much broader than psychotherapy

Dr Reader You had a question Dr Cattell?

Dr McKeen Cattell Dr Wolff mentioned the usefulness of coffee in connection with some headaches and I presume he was referring to caffeine I was wondering about other central stimulants What about amphetamine is that effec tive?

Dr Wolff Dr Cattell it isn t clear to me just how caffeine works I think it is reasonably safe to say that it is effective in some persons Whether it is by virtue of the central excitatory effect or of some effect on vasomotor structures per se I do not know

Dr Cattell I suppose the same may be said of theophylline

Dr Wolff We have evidence to show that caffeine by mouth can cause vasoconstriction Whether it does some-thing centrally as well to interrupt the whole pattern of the attack is the part I am not sure about Benzedrine helps a certain number of individuals

Dr Reader Are you opposed to combining caffeine or Benzedrine with aspirin as is so commonly done not only by the drug companies but by the pharmacies of hospitals across the country?

Dr Wolff It is a matter of temperament I don t enjoy mixing things that way but other people do

Dr. Reader: The reason I asked is that the point was made in the student lecture this morning that it was unwise to mix them because only a small percentage of headaches is affected by caffeine. Aspirin should therefore be given alone, and when the effect of caffeine is desired, that should be given alone. Would that be your opinion?

Dr. Wolff: That would be my preference.

Dr. Seymour H. Rinzler: Dr. Wolff, I think the point comes up in the minds of practitioners as to when chemotherapy should end and psychotherapy begin in these patients with recurrent headaches. I suppose it depends a good deal on the willingness of the patient to end chemotherapy and begin psychotherapy. When should the doctor say to himself, "We have gone as far as we can with medications; now let's get down to something about life situations"?

Dr. Wolff: I confront the patient with this aspect of the problem the first time I see him. I tell him that we have agents that are useful in stopping attacks, but that these will in no way help him in overcoming his problem of continuing to have headaches. Armed with this thumbnail sketch of what the headache is about, and the setting in which it occurs, an individual can do a great deal if he sets about it. It helps many people to have a statement about the nature of the attack, what hurts, what the major drives are, and what can be done about them. I don't think an individual should simply be given the medicament without a full statement of what the problem is or what part, it is hoped, the medication will manage. A good many people, when satisfied that they do not have a brain tumor, are not interested in what they consider the complicated aspects of the syndrome and will let it go at that. But thoughtful people, and many of these are thoughtful people, look into themselves and take pride in being able to master their situation a little better. I am not convinced that extensive, elaborate psychotherapy has proven very valuable in these cases. We can all point to our failures. I know individuals who have been intensively dealt with therapeutically for years without much improvement and others who have been seen only one, two,

or three times who are much better or have lost their complaint

Dr Gold By extensive psychotherapy do you mean thoroughgoing psychoanalysis or something else?

Dr Wolff Yes it includes psychoanalysis

So much for that When should one stop giving ergotamine? If a person has headache every day there is no longer any place for this medicament That person is usually depressed and in most instances needs hospitalization He needs to be taken out of his environment and placed either in a general ward or elsewhere given a chance to sit apart from his problems for a while at least for several weeks Such an interruption may end that series of attacks In this period he will have had time to talk things over look at his situation and have the problem reviewed with him It is not a happy solution for a patient with migraine simply to take ergotamine once a week However there are people who refuse all other help and there are those who become addicted to drugs just as they become addicted to an atmosphere of stress They need it to keep themselves whipped up They take far more of the agent than is indicated They think somehow it is going to prevent the attack To answer your question no patient with vascular headache whether the pure migraine type or not should be turned loose with an analgesic or vasoconstrictor Every patient should have explained to him the dynamics of the attack something about his own nature and the nature of his relation to his life situation and fellow men

Visitor What about the use of small amounts of barbiturates in these people who are very tense in conjunction with the other medicament?

Dr Wolff That is often a help in getting you and the patient connected He may be more relaxed and able to talk more readily It is also remarkable what a placebo will do If the patient comes away with a box of pills and an awareness of your interest in him he often enough becomes amazingly tranquilized and is able to go ahead I am not sure the

barbiturate you mention is having only a pharmacodynamic effect, it may be largely suggestion

Visitor What about alcohol?

Dr Wolff It is an interesting thing about people with vascular headaches that they seem to be sensitive to the action of alcohol in the sense that they often enough have the headache precipitated by alcohol the highball, the vaso dilator People having many headache attacks sometimes try to get relaxation through a cocktail before dinner Most often the result is not good, although they feel rather pleasant at the time, they are apt to have a headache later in the evening

Dr Gold Dr Wolff, you have discussed the vascular head aches Would you say more about the other varieties?

Dr Wolff I mentioned that there are two others and I think I ought to say a word about the muscular type because that may be bothersome enough to call for special attention It is due to the sustained contraction of the large sheet of muscles that runs over the top of the head around the neck, and over the shoulders and back It gives rise not only to the uncomfortable feeling as though one had a cap on or a band, or as though one s head were being squeezed but gives rise to one other very disagreeable effect which frightens people very much namely, dizziness or vertigo This I believe to be due to the actual effect of the cramp of the muscles in the back of the neck, because I have been able to show in these patients repeatedly that if you squeeze the tender muscles with your fingers you can sometimes induce vertigo I look upon this as a spread effect of central excitation from the barrages of afferent impulses coming from the upper cervical region very much like seasickness or the spread effect of a blow on the head, which may make one see stars or sparks Whether I am right or wrong about the explana tion, the discomfort may be strikingly relieved and the vertigo may disappear after a simple manipulation Take the indi vidual s head in your hands one under the chin and the other on the back, and pull the head, rotating it from side to side, and gradually manipulating it in this fashion until the muscles seem to give a little bit I mention this because

it is an exceedingly simple technic and if the muscle component happens to be a conspicuous one a dramatic effect will be demonstrated before you leave the patient s bedside

Dr Gold Would you add to the list of agents for the treatment of headache procaine injections into the muscles and ethyl chloride spray?

Dr Wolff Injection of procaine is certainly capable of reducing the pain in the head in many instances I believe that experts can do this with very little danger but many of these headaches are in the back of the head and in the deep muscles of the neck and there the injection carries more risk We have seen a case with brain stem damage as a result of the injection Such an accident is very frightening and I am not sure that it is worth the price since much can be accomplished without such injections Other parts of the head further away from the foramen magnum are safer places for injections of procaine and some people are enthusiastic about their effects Sometimes headaches result in the back of the head from the involvement of muscles lower down in the back These can be safely treated with procaine injections I am less certain about the ethyl chloride spray I am not sure that it is more than suggestion but possibly it is

Visitor Do these headaches persist as long as the life situation and the forces remain regardless of the number of years?

Dr Wolff If you mean by forces the way the individual looks at his life situation the answer is yes They can remain unchanged over a lifetime but people are extraordinarily plastic and by and large individuals can change in the way they look at their situation They can change their attitudes and sometimes what was once intolerable becomes acceptable What was once thought important is no longer important and people improve spontaneously It is common to have these headaches diminish in middle life possibly for elaborate physical chemical and endocrinological reasons but mainly because one gets to be a little bit more relaxed about life At middle age we are not so sure we

need all the things we once thought we needed. So to answer your question, the personality pattern of a person having migraine can last a long time. The pattern includes the need to be approved, to do as well as one can, not to be found wrong, to excel, to surpass, to be right on all things. These are apt to last a long time.

Dr. Reader: Dr. Ray, is there any drug that is useful in treating trigeminal neuralgia?

Dr. Bronson S. Ray: I don't know of any that is very useful. Vasodilators have been found of some use in that kind of neuralgia.

Dr. Reader: Nicotinic acid?

Dr. Ray: Yes, presumably it improves the blood supply and that in turn implies that this form of neuralgia has something to do with an impaired blood supply.

Dr. Wolff: Dr. Ray, one hears a good deal about the surgical treatment of vascular headache. I wonder if you would say a word about that.

Dr. Ray: There has been a good deal said and written about it. Only recently I made an attempt to review the important things that have been published on the matter and to add our own experience, impressions, and leanings To sum it up in a few words, there are no nerves, single or in groups, that you can expect to interrupt by any means, temporarily by injection or permanently by cutting, that have any important relation to headaches we have been discussing here today. You will find occasional enthusiasts for sympathectomy. They start with the premise that if vascular headaches have something to do with altered vascular tone, all you have to do is perform a sympathectomy and you stabilize the tone of the blood vessels. But sympathectomy has not worked that way for migraine or any of the other vascular headaches that we know of in the head or face. There have been operations performed for dividing the trigeminal nerve. Were the headache limited, for example, to a specific region, an area supplied only by the trigeminal nerve or its sensory root, then division of the trigeminal nerve should relieve it. Not many cases have been done, but

patients who have had trigeminal neuralgia and migraine have been studied, and on the whole it seems not to be a useful procedure because there are other pathways for the vascular type of pain In any case the headache soon extends into areas outside the trigeminal distribution or at least it comes to light as existing in areas outside the trigeminal distribution One of the most recent developments in attempted surgery of headache has been the section of the petrosal nerve, particularly for the so called Horton syndrome in which the pain is limited to a local region about the eye and the nose with excessive tearing and reddening of the eye It was thought that sectioning of the petrosal nerve might be of benefit as it is known that many of the functions implied in this syndrome have pathways through this nerve I think it has not proven to be the case, and there are certainly great disadvantages to section of the petrosal nerve

A simple operation that has often been tried has been the resection of blood vessels particularly if the headache is a fairly localized one in the frontal temporal, or supraorbital region or occasionally in a local occipital area Resection of the arteries in that region has seemed to be something that might be reasonably tried I am not sure that Dr Wolff and I are not responsible for this kind of thing because some years ago while the experimental work was going on, we did resect vessels in a number of places and we found that it sometimes produced beneficial effects but they were always temporary and the pain always recurred within six months, if it was relieved at all It is only what you would expect After all, you cannot completely devascularize an area, and we have reason to believe that afferent nerves supplying the blood vessels grow in just as rapidly as blood vessels do Again to put it briefly, we know of no kind of procedure for interrupting nerves, either temporarily or permanently, or even resecting parts of the blood vessel systems that has the slightest application in the great majority of cases As an experimental procedure it may occasionally

be tried with some justification, I presume, but it is more likely to fail.

Dr. Edward A. Wolfson: Is a headache of 6 or 8 weeks' duration likely to be a vascular or muscular headache?

Dr. Wolff: A headache that goes on for months or years is likely to be a muscle contraction headache punctuated occasionally by an attack of vascular headache. The individual is apt to blur his description of the two when he tells about them.

Dr. Gold: Are you in a position to say what is the common variety of headache that occurs in patients with hypertension?

Dr. Wolff: I think it is a combination of vascular and muscular headache, the vascular component being not necessarily inside the head but outside, like other headaches of the migraine type. It is not necessarily related to the changes in systemic blood pressure.

Dr. Gold: The inhalation of trichlorethylene has in the past been advocated for an attack of trigeminal neuralgia. Is it no longer thought to be useful as a means of helping a patient out during a bad night? If you think it has value, would you say just how you would use it?

Dr. Wolff: Trichlorethylene comes in pearls, like amyl nitrite. The individual breaks a pearl in a handkerchief and in the lying-down position smells cautiously. It makes the person feel light-headed and faint. The drug is inhaled until the contents are odorless. It brings considerable relief for a time. It might make it possible for the individual to get some sleep. The next day, if the patient is having a bad time, he should be admitted to the hospital. Patients with trigeminal neuralgia who enter the hospital usually begin to pick up from that moment. They come into a protected neutral environment. The frequency and intensity of the attacks diminish, and then is the time to decide whether or not the patient should be operated on. The issue is how severe, how often, how long, the age of the patient, and how much is the individual willing to sacrifice in the way of a sensory disturbance in the tissues of the face. The trichlor-

ethylene is of great use in making a dreadful night tolerable but not as a steady therapeutic agent

Dr Ray Some people don t seem to get much benefit, and some develop a tolerance A great many rely on it for the acute episode of pain It might be compared with the use of ergotamine for that type of headache It has a very limited use, and it is not at all curative

Dr Frank C Ferguson, Jr In relation to Dr Gold s question on hypertension, does the level of the blood pressure have any bearing on the occurrence of the vascular headache?

Dr Wolff Only half of the persons with hypertension have headache The level of the blood pressure is no higher in those who have headaches than in those without headaches Furthermore, patients often lose their headaches as the blood pressure progresses to higher levels

Dr Ferguson I believe you used to feel that it was not the caliber of the vessel but the pulsations which were responsible for the pain Am I quoting you correctly?

Dr Wolff I am not sure about that The thing that seems to hurt is the nondistensibility of the blood vessel wall which is dilated and edematous At the same time there is a lowered threshold of the tissues about them The mechanism of the noxious stimulation may, I think, be viewed as disturbed or distorted sensory endings in and about the blood vessels

Dr Ferguson The personality you described Dr Wolff, for the person with headache seems much like the personality with peptic ulcer Do the two commonly occur together?

Dr Wolff Very often Peptic ulcer and headache are commonly found in the same person

Dr Reader Dr Aldridge do you have a question?

Dr John S Aldridge Dr Wolff, I saw a patient in the clinic who had not been relieved by ergotamine and was given shots of morphine I have wondered about that

Dr Wolff That is very bad management An individual in such a plight should no longer be an ambulatory patient He should be hospitalized and the whole matter reviewed

Morphine in such a person is really preparing the patient for a life of addiction

Dr Reader Our time is up

SUMMARY

Dr B B Roy The discussion in the conference this afternoon probed into some of the clinical problems of headache and elaborated refreshing orientation in regard to the nature and treatment of headache The conference developed around the position that the vast majority, about 95 per cent of cases of headache involve mechanisms which are completely reversible, a type depending upon constriction and dilatation of head vessels, another due to sustained contraction of muscles of the scalp and neck, and a third in some way related to disturbances in the upper respiratory passages nose, and sinus Among the so-called vascular headaches the clinical symptoms may vary from very little pain of only a few minutes' duration to attacks of excruciating pain lasting many hours, associated with disturbances in vision sensation, motor function, and the appearance of edema resulting from the constriction of various vessels of the brain For the correct appraisal of such symptoms it is worth noting their severity which might suggest organic disease while bearing in mind their functional nature and reversibility Details of treatment were elaborated, attention being directed to the place of a mixture of carbon dioxide and oxygen caffeine, aminophylline, ergotamine tartrate, aspirin and other coal tar analgesics, codeine, morphine, procaine injections ethyl chloride spray, nicotinic acid and trichlorethylene There was strong warning against the use of morphine in the treatment of even the most severe headaches in view of the high tendency to recurrence There was some interest in the headaches which occur in hypertensive patients The point was developed that half of these patients are without headache and that the headache bears no relation to the level of blood pressure The status of the various surgical procedures which have been advocated by some for the treat

ment of the vascular headache was summed up The belief was expressed on the basis of the literature and personal experience that little can be anticipated at the present time from these surgical measures by way of significant relief from these headaches A question was raised concerning the factors which set into motion the vascular unrest accounting for the headaches It gave rise to provocative comments concerning the role of the personality and psychic factors, both conscious and unconscious One contention was that underlying these headaches are bursts of impulses coming from unconscious material of a conflictual nature aroused by life situations and that these are responsible for the ensuing vascular mischief It seemed clear that there are no drugs which hold out anything more than temporary relief for the common headache, and that only through methods that will yield more satisfactory psychological adjustments can these problems be brought under more enduring control

The Doctor's Bag Revisited

Dr. George G. Reader: This afternoon we are going to look into the doctor's bag. Our last look was back in 1942, and it became the first conference in the annual volumes of the Cornell Conferences on Therapy. Dr. Gold opened that meeting by describing what he found when he stopped doctors in the hall and asked to see the contents of their bags. Some of the people were quite embarrassed, for only one or two of the bags gave evidence of careful planning. We are fortunate, though, in having back with us again today the owner of one of those bags.

Dr. Guion, would you start by telling us what is in your bag and how you use the things you carry?

Dr. Connie M. Guion: What you carry in your bag depends on the kind of practice you do and where you do it. I have a general family practice here in New York City, where help is readily available in emergencies. The previous conference on the doctor's bag emphasized the items that should be at hand when there is urgent need for action.* I believe it lists some 30 drugs that might be decisive in emergency situations. If we set out to make another list, I think we would find that only a few changes have taken place.

Today I shall demonstrate my bag as it is outfitted for the home care of my patients here in New York. In New York City it is surprisingly difficult to get service in drug stores at night or on Sundays. You'll find that I carry extra supplies for my patients' convenience. There are some

* "The Doctor's Bag," *Cornell Conferences on Therapy*, Vol. I, 1946.

emergency items here, but I've left out many things important in a practice with a great deal of emergency work

I should like first to show you the instruments I carry One of the most important is a light, and if you have a combination ophthalmoscope and otoscope, you can use the handle for the illumination of the throat or any other area A second important thing is a thermometer I carry at least two, and when I am seeing a number of infections, I have as many as four If you clean the thermometers yourself, you'll keep them longer, for patients have an uncanny way of washing them under the hot water tap

Then I have a blood pressure apparatus and stethoscope with a separate bell and diaphragm so I can listen to patients who are not to be moved Tongue depressors are convenient, but you can always use a spoon or the handle of a fork I like to have a pair of nasal forceps for Dowling packs

In these two steel cases I carry two sterile hypodermic syringes, one with a small 26 gauge, 3/4 inch needle, and one with a longer 1½ inch needle, a No 22 To sterilize the skin I have a bottle of 70 per cent alcohol I have this extra set of sterile needles in 70 per cent alcohol

Whenever I am giving a lot of penicillin, I carry these individual cartridges with me The one I happen to use, Duracillin has a simple syringe and a disposable needle, thus eliminating transmission of infection

Very often blood counts are important, and I carry this little box with alcohol, a red and white pipette, slides and extra bottles in which to put blood samples

I have an accessory bag in the back of my car, which contains a stomach tube, a nasal tube, and a catheter It has extra tourniquets for in some cardiac patients you may want to use tourniquets on all four extremities

As to drugs, each person has to make his own selection Mine is arranged in a plastic box which is conveniently divided into sections First there are drugs for the common cold, I carry antihistamine combinations, Coricidin and Chlor Trimeton, which I like because I am accustomed to using them Then, for Dowling packs, I carry a fresh solution

of 10 per cent Argyrol I also carry a nasal solution of an antihistaminic of some type For patients who have colds and are aching a good deal, there is aspirin or aspirin in some combination such as the APC or Empirin compound

There are a number of antibiotic preparations that are useful to have along Chloramphenicol was my stand by until the reports of blood dyscrasia appeared I now limit it to the diseases in which it has a demonstrated advantage I carry vials of procaine penicillin and tablets of Gantrisin Also here is erythromycin and some form of either Terramycin or Aureomycin Which one is in my bag at a particular time depends on the infections that are going about

The next group of drugs is my collection of sedatives I usually carry several kinds, sodium pentobarbital, which we use here in the hospital, Seconal, phenobarbital, and Tuinal I have a few of all of these to satisfy individual tastes for I think it is most important to leave patients with a sense of comfort and not to make them wait for relief while the family hunts a drug store

Next I have narcotics morphine, codeine, Demerol Pantopon, and Dilaudid Some patients are sensitive to morphine or Demerol and not to one of the others

Then I carry a tube of apomorphine in case I see a person who has swallowed poison Apomorphine by hypo, 1/10 grain is very effective in emptying the stomach

I have Adrenaline in two strengths, 1 1000 and 1 2500 and also Adrenaline in oil, 1 500 A very small dose is measured more accurately with the dilute solution while the *Adrenaline in oil gives a prolonged action*

Among the miscellaneous things, I keep ergotamine tartrate, because I have a good many patients with migraine and a small tube of Aureomycin ointment

Here are several vials of vitamin K Many doctors keep insulin in their bags I don t carry insulin

In the cardiac section I have vials of ouabain I prefer that to any of the other intravenous medications because I am accustomed to using it Some carry lanatoside C, but this happens to be my choice I also have ampoules of amino

phylline, both 0 24 and 0 48 Gm , and Mercuhydrin 1 and 2 cc

In the other bag from the back of my car I have a bottle of isotonic sodium chloride, one of 5 per cent glucose in water, and one of 50 per cent glucose There are packs that go with them, one for intravenous and one for subcutaneous administration Here are parenteral vitamins that can be added to the fluid It is important to have fluids available, for you may not be able to get them when you need them

Oftentimes you find people who have acute bursitis, lumbago, and various kinds of pains Ethyl chloride spray is effective, at least temporarily, enough to let them move about and get the physical therapy that you may prescribe

I think that covers my bag, Dr Reader

Dr Reader Thank you, Dr Guion Perhaps we should ask for comments on the things that you carry before we go on

Visitor I was wondering whether you have anything to test for acetone in the urine?

Dr Guion I usually carry Eli Lilly s outfit for determining acetone and sugar I haven t one in the bag at the present time

Dr Harry Gold Dr Guion, what is your thought in leaving insulin out of the bag?

Dr Guion I think it is because I practice right here in town If I have anybody with sugar in the urine and a clinical picture of coma, I send them directly into the hospital I think a bag has to be a sort of base from which you work You cannot carry everything in your bag

Dr Reader How often have you seen a patient in coma where you thought you might have given insulin?

Dr Guion I may have sent half a dozen into the hospital

Visitor Don t you use a lumbar puncture needle?

Dr Guion I have a lumbar puncture needle here, but I have not used it in a long time It is a very small thing to carry I just forgot all about it Incidentally, it can also be used for aspiration of the chest Having it right at hand with the 50 cc syringe might save the life of a patient with tension pneumothorax

Student: Do you carry a microscope to do your blood counts?

Dr. Guion: No, I usually wait until I get back to the office.

Dr. Reader: I understand that in one of the medical schools they do actually equip students with a portable microscope when they go out expecting to do a count in the home. We have not felt that was necessary in our home care program. I wonder if many people in practice carry a portable microscope.

Dr. Guion: I never saw a patient whom I could not get into the hospital fast enough for a blood count or even to have the spinal fluid examined.

Dr. Reader: Someone once said that doctor's bags are like attics. You start out with a few items, but after several years you find them crammed with all sorts of useless things, and then you have to throw out everything and start over again. Let me ask you, do you stop every 5 years and think how you might revise the contents, or do you just revise it as you go along, or how do you handle that problem?

Dr. Guion: As a matter of fact, I find that I have to refill mine practically every night. Before I go to bed, I fix it so that it is always ready.

Dr. Reader: You look it over to see what might have been used up that day. Are you constantly reviewing its over-all contents as well?

Dr. Guion: Yes, I remember the time when I used always to keep camphor-in-oil and Coramine in my bag, but I don't carry them any more.

Visitor: Would Dr. Guion give us any ideas as to what she might add to her bag if she were practicing in a rural community without a hospital near by?

Dr. Guion: Yes, you would have to carry insulin and other medicaments, something for the eye, and a larger supply of intravenous fluids. I've found that drug stores in small communities are conscientious about having somebody on duty at night, and you can get things nowadays very easily in rural districts.

Dr. Reader: The bag you carry in the back of your car

interests me. It seems to be a compromise between preparing for any emergency and carrying half your office with you. Certain basic equipment can be in the bag that you carry all the time. Other things can be put into your bag only when you go out on a call where you will face a particular problem, or they can be carried in a second bag readily accessible in your car but not making the load in your hand heavier.

Dr. Guion: Yes, I always try to find out what is the matter with the patient, and then I go prepared. For instance, if I were told that the patient was in coma, I would be much more inclined to carry some insulin with me. The equipment for lumbar puncture and catheterization I would put directly in my main bag. If I were told a patient was blowing bubbles, I would go prepared for the treatment of a pulmonary edema.

Visitor: Is there a role for a small surgical kit in your bag?

Dr. Reader: You mean to control hemorrhage?

Visitor: Hemorrhage or, for instance, to perform an emergency tracheotomy.

Dr. Guion: I think if I had a real emergency tracheotomy I would do what I saw them do at Johns Hopkins when I was visiting there one day. A woman on the ward suddenly became blue. One of the well-known medical men pulled out his pocketknife and cut a hole in her throat, and somebody else stuck in a fountain pen until they got a tube. I don't think you can carry everything. If you get pushed too far, you have got to use your ingenuity.

Visitor: Do you feel that a small cylinder of oxygen would be appropriate?

Dr. Guion: No, I don't think so. I have never seen a patient I had to provide oxygen for. You can get oxygen quickly here in New York. If I were in the country, I think one of the cylinders of oxygen from a basal metabolism apparatus would be very convenient.

Dr. Reader: I wonder if we might ask some of our practitioner alumni if they carry bags that differ from Dr. Guion's?

Visitor May I say something as an old classmate of Dr Guion s? She believes in ouabain which one would expect as a disciple of Dr Cary Eggleston They were teaching that forty years ago Of course, the difficulty is that you can t get samples of ouabain I am surprised she is not using other cardiac remedies because we get them handed to us by every detail man that comes around

Dr Theodore Greiner Maybe the ouabain in Dr Guion s bag could be the result of old teachings but the reason she gave for having it seems to indicate sound judgment in the matter of injecting digitalis The number of glycosides presented to the doctor in ampoule form is steadily increasing It s hard to avoid confusion unless you remember that they all have the same action on the heart Where they do differ is in the practical details of administration the size of the dose, the time the action comes on, the minimal safe interval before injecting another dose That means each glycoside must be injected on an entirely different dosage plan Yet the occasion for parenteral digitalis is a very rare one in a well run practice Dr Guion likes ouabain because she is used to it If you add to your bag each new remedy the detail man brings around you'll never be secure with any injectable digitalis As far as ouabain is concerned, it is one of the rapidly acting glycosides Retail stores may not keep it in stock, but they can order it from Eli Lilly or Varick

Visitor I am surprised at a woman carrying four special tourniquets with her Nylon stockings make excellent tourniquets in an emergency

Visitor In respect to intravenous therapy I don t find it necessary to carry 5 per cent glucose or normal saline in a community smaller than New York I feel the only indication for intravenous therapy is shock, and that a plasma expander is better than either of these solutions

I also hearken back to the days when I was told by Dr Gold, who is sitting up there in front that Coramine and caffeine sodium benzoate should be thrown down the sink However, they fill pyschological needs when something must be done for a patient who is breathing her last These

ampoules are helpful when we have to be governed by what the family thinks.

Dr. Reader: Perhaps it does you some good even if it does not help the patient.

Dr. Guion: I have some caffeine sodium benzoate here. If the situation demands, I could use it. I don't use it very much.

Visitor: What about sterile dressings? What do you do if you come across somebody who has a burned hand?

Dr. Guion: I have some sterile dressings in here. I don't use them very often, and I forgot about them. I also have a roll of bandage.

Visitor: Do you ever find it necessary to do a lumbar puncture at home?

Dr. Guion: Yes, occasionally a patient is in coma at home, and I want to know whether he has had a hemorrhage or not.

Dr. Reader: I supose you don't try to do a manometric, but only get a little fluid for study and see if the pressure seems to be increased.

Dr. Guion: Yes.

Visitor: I should like to ask Dr. Guion if she finds it necessary to carry finger cots or rubber gloves with her, and whether she carries a speculum for female examination.

Dr. Guion: I don't carry a speculum. I have a rubber glove here that I have to use now and then.

Visitor: Do you carry a lubricant for it?

Dr. Guion: No, I find that water is very good, and I also go to very few places where there isn't petroleum jelly or cold cream. If I can't get those, I go into the kitchen and get a little salad oil.

Dr. Gold: I wonder whether Dr. Guion would outline the advantage of a general practice bag over one which carries the minimum amount of material necessary to meet emergency situations, that is, those in which you cannot easily come by these medications without actually having them along with you.

Dr. Guion: I think it is important to be able to relieve a patient of his symptoms when you see him, because diagnosis

is often a slow process Yesterday afternoon I saw a woman who was very upset about going into Memorial Hospital today for an operation Since she lives all alone, there was no way for her to have gotten any sedative I gave her a Tuinal capsule Inside an hour she was relaxed, and she had a good night s sleep I am sure she went through the mastectomy today with more fortitude than if she had been awake all night

Dr Gold I wonder whether a situation like this might not usually be handled more satisfactorily by hypodermic injection of sodium phenobarbital or one of the narcotics If it is imperative that the patient should have a comfortable night's sleep prior to an operation, one has to make sure that the medication is sufficient for the purpose It is then well to give a dose and wait to see its effect, and give more if necessary The advantage of the hypodermic injection is that it only takes 10 or 15 minutes to find out whether the dose is adequate or more is needed, it takes much longer in the case of the oral dose There is also the danger of losing the drug by vomiting I would think that in general the hypodermic route would be preferable for an isolated situation which demands the assurance of a good night s sleep

Dr Guion In handling this woman, I had no fear of her vomiting I feel that the opiates induce nausea and vomiting so often that I would not have given her an opiate under any circumstances She might not have gotten sick at the stomach until two or three at night Another popular injection to make people sleep is Demerol As I have watched the effects of 100 mg of Demerol, I feel that it is not as good a hypnotic as 0 2 Gm of sodium pentobarbital Furthermore I did not want to give this woman a hypo in the state she was in I felt that if I gave her a reliable oral hypnotic she would go to sleep and have a good night s rest, which she did

Dr Reader Before we go any further, I would like to ask Dr Milton Levine to tell us about the bag he uses since the practice of pediatrics makes certain requirements other than those described by Dr Guion Then we can go back to discussing the general subject of the use of the drugs

Dr Milton I Levine After Dr Guion s demonstration, you are going to be very much disappointed to see what a pediatrician carries, at least one practicing, as I do, in the city of New York Children always have their parents nearby, and you can always send them out for what you need At night I have occasionally gone myself and picked up things I thought were necessary Only once did I ever have to use the 5 per cent glucose solution in a child, and that was in the case of a baby who was severely dehydrated and whose parents refused to let him be taken to a hospital I was able to find a drug store that had the material The only thing I carry in my car besides my regular bag is a stomach pump, which I have used only twice in the course of my practice of about twenty five years, once on a child who took a bottle of oil of wintergreen, and the other time on a child who ate a box of Ex lax tablets

The contents of my bag changes occasionally In the early days I used to carry one of those hand scales with me Al most everybody borrows a scale through the diaper service nowadays We pediatricians used to carry myringotomy knives, for we saw many cases of purulent otitis media Per haps half of the acute upper respiratory infections have some effect in the ear Antibiotics have largely displaced the myringotomy knives from our bags I formerly carried a lumbar puncture needle, but I gave it up after some years

Looking inside my bag, I see the stethoscope, the percussion hammer, the otoscope, and the ophthalmoscope The otoscope is extremely important in pediatrics for inspecting the throat as well as the ear I find it is most important to keep a spare bulb, for if your bulb burns out in a patient's house, you are lost, and there are very few stores in the city of New York that carry such bulbs Next are tongue depressors Here is waterproof adhesive tape for general use as well as for umbilical hernias so that the babies can be bathed with the strapping on I have three sterile syringes, two with a long No 20 needle for penicillin injections, and one with a small No 26 needle for other injections All syringes are fitted with the Luer Lok

Dr Reader I don't know of a study on hepatitis that has actually traced a specific case to the doctors' bag At any rate the virus is an extraordinarily resistant one Careless boiling or handling of antiseptics is certain to miss the virus I would think there might be advantage in using a pressure cooker

Dr Guion I have been boiling needles for 45 minutes but a pressure cooker seems to me a simple and prudent change

Dr Gold There is a company that now manufactures an office type autoclave for about $300

Dr Reader I was interested in the comments about antiseptics Dr Guion uses 70 per cent alcohol and Dr Levine occasionally uses whiskey I was thinking, is it not more practical to use one of the detergents? If you were caught in the home, perhaps one of the soap powders would be more satisfactory than whiskey Something like pHisoHex may be better than 70 per cent alcohol to carry in your bag for it does not burn and has a higher bactericidal action than 70 per cent alcohol

Visitor As an internist practicing in the city, what do you think of a portable electrocardiograph? If a woman calls you to see her husband who has had substernal pain, don't you think a portable electrocardiograph is essential?

Dr Guion I think a portable electrocardiograph apparatus is very important I have one which I use when necessary but I don't carry it around with me all the time

Dr Reader How often have you taken electrocardiograms in the home in the last year?

Dr Guion I should think 25 times

Dr Lawrence S Sonkin If you're going to carry a portable electrocardiograph, it's important to know what type of electrical current is in the home and have a transformer available We blew ours out last week by hooking it into direct current

Dr Reader We have, as you know a home care service in the medical school It is clearly a matter of care at the home itself rather than meeting every conceivable emergency Dr Guion took an active part in planning the bag for students to carry They vary a little from Dr Guion's bag mainly

because we have tried to simplify. We don't have quite as much variety in drugs as Dr. Guion has; for example, only morphine sulfate rather than five kinds of narcotics. We have not tried to meet every emergency because we also have various emergency packets that we can toss into a bag and carry out with us. In the same way we take out the portable electrocardiograph only when we expect to use it.

Dr. McKeen Cattell: I was wondering about the digitalis preparations.

Dr. Guion: I mentioned the ouabain ampoules. Usually I carry Digitaline Nativelle or Digitoxin as well. I use the Digitaline Nativelle because it is pink and has a "D" on one side and an "N" on the other, and you can be certain a patient won't mix it up with some other little white tablets.

Dr. Cattell: But you would want to carry them with you in your bag?

Dr. Guion: Yes, I carry them for all but the most extreme emergencies. Except for days like today, when I ran out of them.

Visitor: I notice that no rapidly acting vasodilator was mentioned, such as amyl nitrite. That may be very valuable to relieve the crushing pain of an anginal attack.

Dr. Guion: I think nitroglycerin acts just as rapidly if you put it under the tongue. I always carry the hypodermic tablets because they absorb more rapidly than the ones that are put on the market as sublingual. I don't carry amyl nitrite.

Visitor: You can't. It blows up in your bag.

Visitor: I haven't heard sodium Amytal mentioned. I always carry an ampoule for intravenous use in a convulsive seizure.

Dr. Guion: I haven't any Amytal, but I have sodium phenobarbital.

Visitor: I have read that ethyl chloride can be used as an anticonvulsive. I was wondering if anyone could tell me how.

Dr. Reader: Pediatricians used to like it for myringotomies. Did you ever use it, Dr. Levine?

Dr Levine We used to use it because a single whiff of it was usually adequate The moment the child went under you performed the myringotomy As to the convulsions of children, usually the child is out of a convulsion by the time you get to the house Most convulsions accompany a high temperature, and you simply bring the temperature down Severe repeated convulsions can usually be stopped by sodium Amytal intravenously

Visitor Then the ethyl chloride can be used as a general anesthetic for meeting the emergency of convulsions?

Dr Gold Yes, you drip it on a cloth and hold it over the face, just as you anesthetize with ether

Visitor How safe is that, Dr Gold?

Dr Gold It is moderately safe I can remember years ago in the Hospital for the Ruptured and Crippled the students giving anesthesia always started with ethyl chloride and then continued with ether I don't think it is a generally approved practice now

Dr Greiner Ethyl chloride gradually lost its appeal as the tragedies from its use were recognized The anesthetic effect comes on so quickly that the respiratory center may be depressed without warning Its margin of safety is much smaller than that of ether I understand it also sensitizes the heart muscle like chloroform and has led to cardiac death Ethyl chloride cannot be recommended as a general anes thetic, but it is only fair to remember that it took about fift years of use in the office and home to decide that point Nowadays intravenous barbiturate anesthesia is most com monly used for emergencies outside the hospital It is clean and easy, but when enough experience has been gathered, it may turn out to be no safer than ethyl chloride The few times that I ve had to anesthetize, I ve felt much better for having a little can of ether handy

Student Dr Levine had three or four books in his bag One looked like a good sized leaflet Do you take your histories in those books?

Dr Levine In one I make a complete record of every patient I see in the course of a day It is loose leaf and the

record is later filed with the patient's charts The second book is just a duplicate of my appointments in the office, so that I know what time I have free and what time I have not Then the third one is a book which contains certain information about the more recent drugs that I might wish to turn to

Visitor I think we might remember that women do menstruate and miscarry, and that in general practice we must provide for emergencies along those lines

Dr. Reader Do you carry any of the endocrine preparations, Dr Guion, to control a threatened abortion, for instance

Dr Guion: No, I don't I see such patients once in a while and what I do is to call up an obstetrician at once So far as severe menstrual pain is concerned, I usually give them an Empirin compound with some codeine and then let them carry on I don't consider it an emergency

Visitor When I was in practice doing obstetrics, I always carried two pairs of sterile gloves 2 sterile medium sized specula, uterine packing forceps, sponge, and iodoform gauze in glass jars The public can t smell some of the new antiseptics, but iodoform impresses them with the fact that you are being careful So it s reassuring for the family as well as the patient. Occasionally you will have to put in an intrauterine pack or pull out a wad of placenta, and you can be doing that while waiting for the ambulance

Dr B B Roy I am from India I appreciate that the contents of the doctor s bag must be suited to local needs and personal preference of the practitioner However, I was amazed at the multiplicity of drugs Dr Guion carries in her bag and the number of bags she carries in her car Perhaps most practitioners have a doctor s bag, not all doctors have a car This I mention because the messages from the Cornell Therapy Conferences are relayed to distant lands and are eagerly sought for. From this point of view it is important to limit the number of drugs in the bag, but to expand our knowledge in regard to putting these few to more effective use and wider application For instance, Dr Guion,

you have all the antibiotics in your bag in addition to other chemotherapeutic agents If it is a question of an overnight affair, would you not reduce these to one or two and indicate to our distant colleagues which one or two could be pressed into service for most purposes? To include a large number of a particular group of remedial agents will merely help to confuse the very people we are trying to inform My plea is to decimate the number but to disseminate helpful information for their extended use After all, you cannot carry a drug store around with you

Dr Guion I think what Dr Roy says is true The contents of your bag are a personal matter If you practice in the country, you have to be prepared for all sorts of emergencies In the city where you can get such things you just carry in your bag what your practice would demand day by day and I think you have to decide that from personal experience

Dr Roy I will agree to that Dr Guion, I know you appreciate the fact that it s easy to add to the contents of the bag, but it really takes the experience of a conference like this to show how we can manage with much less We still have the question, what essential things we can carry to see the patient through a certain period

Dr Guion I think what I carry in my small bag is really sufficient for that

Dr Roy I will say it is more than sufficient Of course local conditions will modify the contents of the bag But the point I am trying to make irrespective of the area or nature of practice, is whether it is really necessary to load the bag with so many drugs of any one category, be it antibiotics or barbiturates or opiates Dr Guion would it not be enlightening to have a selected few and emphasize their wider application? In my own practice, there are things I would have to add and others I would reduce to a considerable extent

Dr Guion The choice of which drug to use is a general problem in medical education At any rate, you must pack your bag according to your personal experience

Dr Reader Our time is up

SUMMARY

Dr Greiner On our revisit to the doctor s bag twelve years later we found diagnostic equipment and basic drugs for emergencies were much the same as at our last visit In its second function of providing for the care of patients in the home the bag reflects the rapidly changing face of medical practice Antibiotics are now the most prominent feature in the drug section There is increasing preoccupation with chronic disease recognized in discussion of the portable electrocardiograph new and old cardiovascular agents and the patch test for tuberculous children Some bags contain articles with the sole purpose of satisfying emotional needs of patients who have come to expect certain articles or even smells from the doctor s bag The role that the bag might play in spreading infectious hepatitis was a disturbing and unanswered question Disagreement arose on where to make the compromise between a bag containing a miniature pharmacy and one that is comfortably portable with a special plea entered by our foreign colleague to make a few drugs serve many purposes Careful planning and discriminating choice can make the doctor s bag a trusty friend instead of a burden Regular review of the contents in the light of personal experience and local needs should control the tendency to accumulate every new item that comes on the market

Management of Poisoning by Pesticides

Dr George G Reader We have been reading a great deal in the popular literature—popular for physicians, I mean—about the danger of the newer pesticides, rat poisons, insect poisons, and compounds for the control of fungus diseases in plants Even the home gardener has access to many lethal chemicals, and numerous reports of poisonings by these materials have appeared In today's conference we will consider the subject from the point of view of the dangers in the use of these materials and what can be done about them Dr Solomon Garb, of the Department of Pharmacology, will open the discussion

Dr Solomon Garb Recently there have been two important developments in the problem of poisoning by pesticides An unfavorable one is the increase in poisonings from insecticides because of their increased use and misuse, and because of the fact that more efficient and more toxic chemicals have come on the market Despite the danger involved, electric vaporizing devices for dispensing insecticides are advertised and sold for use in homes, sleeping quarters, and areas where food is kept Spray insecticides which are toxic and sometimes lethal by inhalation or when absorbed from the skin are widely used without adequate precautions

A second development has been favorable Because of inadequate information on the labels of the containers, a doctor dealing with a case of poisoning was in the past frequently unable to determine the toxic agent Since there are specific antidotes for a number of the poisons used, it is essential to know the composition of these pesticides In a conference on poisoning held previously, Dr Gold called attention to the

need for proper labeling of all substances which may cause poisoning, even though they are not legally classified as poisons * This year we are fortunate to have available a list of the trade names of more than 400 pesticides and household poisons and their constituents This list, prepared by Dr Jay M Arena of Duke University, appears in *Current Therapy*, published by Saunders We hope this valuable list will be expanded in future editions and that it will also include some data, if possible, on the concentration of the toxic ingredients The publications of the A M A Committee on Pesticides also give the trade names of some of the newer pesticides

A large variety of substances are used as pesticides Arsenic, copper sulfate, and mercury compounds are widely used against many pests Rodenticides include thallium, strychnine, cyanides, phosphorus, and ANTU (alpha naphthyl thiourea) The poisons generally used to combat moths are camphor, paradichlorobenzene, naphthalene, and carbon tetrachloride To destroy roaches, phosphorus, sodium fluoride, sodium fluorosilicate, sodium borate, or boric acid are employed Poisons used against a variety of insects include nicotine, ethylene dichloride, DDT, Toxaphene, and Lindane (benzene hexachloride) The organic phosphates, parathion, TEEP, HETP, and E 838 are becoming increasingly important as spray insecticides and as sources of danger to humans

The physician faced with a case of acute poisoning by a pesticide can, of course, proceed with greater confidence if he knows the identity of the poison involved However, the composition of the pesticide is frequently not known when the patient is first seen Nevertheless, if certain routine measures are employed at once, the prognosis may be improved in many acute cases Even when the kind of insecticide is not known immediately, one can usually determine whether the patient was exposed to a spray, or whether he swallowed the poison If a spray is implicated, the first step,

* Conf 1 Household Poisoning I" *Cornell Conferences on Therapy*, Vol. IV 1951

even before completing the history or physical examination is the immediate removal of all the patient's clothing followed by a thorough washing, preferably in a shower Many of the spray insecticides commonly in use can be absorbed through the skin in toxic or lethal amounts, and the patient with pesticide over his body and permeating his clothing may continue to absorb additional poison while in the doctor's office or the hospital Medical personnel should, of course, exercise reasonable precautions in handling the contaminated clothing to avoid being poisoned themselves Ordinary rubber gloves give satisfactory protection The clothing should not be destroyed until the composition of the pesticide has been established

If the poison was swallowed, other measures are indicated Gastric lavage should be instituted without delay to remove any remaining poison from the stomach I know of no contraindications to lavage in these cases, since strong caustics such as lye are not usually present in pesticides After lavage, the use of saline cathartics will probably reduce absorption of any poison already in the intestinal tract Oily cathartics are contraindicated, since they may increase absorption of the poison

If the kind of poison is known, specific treatment can be instituted However, even though the exact nature of the poison is at first not known, careful examination of the patient may suggest its general classification The most important offenders among the spray insecticides are the organic phosphates parathion, HETP, and TEPP These substances are anticholinesterases and are similar to the newer war gases They are widely, and sometimes carelessly, used They are absorbed through the skin, the respiratory tract, and the conjunctiva without any warning local inflammatory reaction Toxicity is high, about 100 mg of TEPP is likely to be lethal for an adult About 500 mg of HETP and 1,000 mg of parathion are probably fatal doses The actions are those of a long acting cholinergic drug, with overstimulation of the cholinergic nerve endings followed by exhaustion and paralysis

Dr Riker, who is in the audience will discuss details of actions and treatment later I should like to point out, however, the importance of identifying a poison as an anti cholinesterase Specific therapy, if instituted promptly, can save people who have absorbed from 5 to 10 lethal doses

Another group of spray pesticides which may cause toxic symptoms are the chlorinated hydrocarbons, including DDT, Toxaphene, and Lindane Fortunately, they are far less toxic than the organic phosphates It requires about 30 Gm of DDT or Lindane to kill an adult About 8 to 10 Gm of Toxaphene would probably be lethal Such amounts are not likely to be absorbed from the skin, and serious poisoning by these agents usually results from swallowing them There are no specific antidotes, but careful, attentive symptomatic treatment will improve the patient s prognosis considerably Like the more volatile chlorinated hydrocarbons these agents affect the myocardium, so that amounts of epinephrine and nor-epinephrine not ordinarily hazardous may pre cipitate a fatal ventricular fibrillation These drugs are therefore contraindicated Also excitement and anxiety should be avoided and the patient kept as quiet as possible Should tremors or convulsions develop they are best managed with phenobarbital

The treatment of poisoning by some of the other pesticides has been discussed in previous conferences on poisoning and I will not repeat the details of these * Perhaps those of greatest interest will be brought up in the discussion

We may also say a word about chronic pesticide poisoning The increasing use of vaporizing devices in homes may lead to many cases of chronic poisoning There are no suggestions for therapeutic measures here other than avoidance of further exposure and treatment of symptoms

Dr Riker, would you comment on the treatment of poison ing by the organic phosphates?

Dr Walter F Riker, Jr I would first like to make a few general remarks in relation to these substances The anti

* Confs 1 and 2 Household Poisoning I Household Poisoning II" *Cornell Conferences on Therapy* Vol IV 1951

cholinesterases as a group are indiscriminate in their action They do not inhibit cholinesterase at a particular site but wherever it occurs Cholinesterase at some sites in the *organism is essential to life*, at other sites it is less vital Cholinesterase may be specific or nonspecific The specific cholinesterase will hydrolyze primarily or exclusively acetyl choline, so it is not unreasonable to expect specific cholinesterase at the strategic sites within the organism

The agents mentioned by Dr Garb will inactivate both specific and nonspecific cholinesterases HETP is a mixture of pyrophosphates in which the active principle is TEPP tetraethyl pyrophosphate Unfortunately, from the standpoint of the present discussion, TEPP has a greater affinity for the specific cholinesterase located within the central nervous system at ganglionic and neuroeffector synapses When the concentration of the specific enzyme at these sites is lowered sufficiently, the consequences are widespread The results are those one would expect from acetylcholine It is easy to review the effects of acetylcholine or a more persistent cholinergic drug like acetyl beta methyl choline and predict with reasonable accuracy the effects that follow inhibition of cholinesterases They include all the so called muscarinic actions of cholinergic drugs That means stimulation of smooth muscle and salivary, lachrymal, and perhaps most important, bronchial glands The heart may be slowed The *central nervous system usually exhibits an* initial increase in *activity which is followed* by depression

The nicotinic effects occur at the motor end plates and at the autonomic ganglia Stimulation of the motor end plate is followed by depression and paralysis Similarly, the autonomic ganglia are first excited, then paralyzed The adrenal medulla may be considered as a ganglion, and considerable epinephrine liberation may be expected

What can be done to combat these effects? First, one must attempt to block the actions of endogenously liberated acetylcholine We assume that acetylcholine accumulates at each of these sites as the neurohumoral mediator and is responsible for producing excitation followed by depression

For those actions classified as muscarinic, atropine is the blocking agent of choice It protects smooth muscle, secretory glands, and the sinus region of the heart from excitation by acetylcholine It also protects the central nervous system, preventing convulsions Atropine does not block the actions of acetylcholine on the motor end plates or autonomic ganglia

At the motor end plate, small doses of d tubocurarine can prevent or reduce the harmful actions of acetylcholine without paralysis of the synapse, but this requires judicious selection of the dose of curare Therefore, I would oppose the use of curare except in experienced hands

If paralysis of neuromuscular junction occurs, protection by atropine alone will not save the patient's life Respiratory paralysis will supervene Therefore, artificial respiration must be given and an adequate airway maintained Here atropine is again useful It inhibits salivary secretion, and prevents excessive bronchial secretion and constriction of the bronchial smooth musculature Insertion of an endotracheal tube will insure a patent airway and provide an easy tidal exchange It is then possible to respire the patient directly by mouth or by respirator

The anticholinesterase action, if it has persisted long enough causes considerable loss of fluid through salivation, sweating and secretion It is therefore important to replace the lost fluid How often should the administration of atropine be repeated? That depends on how long cholinesterase remains inactivated and that in turn depends on the nature of the inhibitor If the inhibitor makes a reversible combination with the enzyme, the latter may be expected to recover within a matter of hours The action of atropine, though it varies at different sites, may persist long enough for a single large dose to protect the effector cells from excessive cholinergic stimulation If, however, the enzyme is inhibited irreversibly, as it would be with HETP, TEPP, or parathion, it is necessary to evaluate the rate of regeneration of new enzyme protein and the critical level needed at each of the strategic sites for normal function Until a critical

level of enzyme is reached, it is necessary to repeat the administration of atropine This may take days depending on the poison and on the sites at which enzyme regeneration must take place The rate of regeneration is different at each of these sites

There is no serious hazard in the use of atropine in the emergency It should be given intravenously and in suitably large doses The subcutaneous dose of 0 4 mg usually given is inadequate It is a small dose absorbed at a slow rate in a situation in which we want maximal atropinization as rapidly as possible I would choose the intravenous route and would give 2 to 3 mg immediately, repeating the dose as often as necessary Central excitation from atropine can occur, but it is unlikely to progress to a serious stage Therefore, I would not hesitate to give large intravenous doses as often as necessary in such an emergency Furthermore, it is essential to recognize that atropine action will be continuously counteracted by the cumulating acetylcholine This in effect will diminish the magnitude of atropine action, and large doses will be reduced to the equivalent of some lesser amount

Dr Walter Modell Dr Riker, how can one tell how often doses need to be repeated?

Dr Riker I would decide that by observation of the patient

Dr Modell Not by determination of cholinesterase levels of the blood?

Dr Riker The determination of cholinesterase levels of the blood will not help us because the serum esterase is a nonspecific type of enzyme produced by the liver Cholinesterase blood levels do not indicate the concentration of enzyme at a specific site such as a central nervous system synapse or a neuromuscular junction The two types of cholinesterase are quite different Since we cannot analyze the specific enzyme at the strategic sites within the organism, we must be guided by observation of the patient, determining his functional capacity at each site

Dr Modell We have given many patients doses of atropine as large as 2 mg intravenously This is large only by com

parison with the usual dose, but not in terms of what it does to the patient. It makes them uncomfortable. They feel dried out. The pupils remain dilated, but I do not recall any patients who suffered severe distress. This point needs to be kept in mind because atropine is of primary importance in this condition. Since the effect is rather long-lasting, for as long a period as 12 hours or more, would repetition of such doses be necessary?

Dr. Riker: The persistence of atropine action is peculiar. It depends on the particular neuroeffector site under consideration. For example, the cycloplegia may last as long as 40 hours, whereas the blockade of the cardiac vagus by atropine will be over in about 3 hours in man. In man and the cat the blockade of the salivary gland is long-lasting in contrast to that of the cardiac vagus. We must therefore consider the elimination of atropine effect in relation to the particular synapse involved. We might not have to repeat atropine to suppress excessive secretions, but we might have to repeat it to suppress excessive vagomimetic action on the heart.

Dr. Modell: You suggested that the anticholinergic action of atropine might not be sufficient to save a person from death and that some other type of treatment is indicated. At what point do you decide to employ additional measures?

Dr. Riker: I meant that atropine does not protect against the actions of acetylcholine on the motor end-plate which, if severe enough, would eventually lead to paralysis. Much depends on the degree of involvement of neuromuscular function. Mild fasciculations represent no threat to life and will disappear. However, if they are widespread, generalized, and intense, a small dose of curare will suppress them without producing any impairment of the transmission process. I would be most concerned with weakness of respiratory musculature as first exhibited by loss of intercostal action. I would then be ready to aid respiration.

Visitor: Once the excitatory phase at the motor end-plate has passed, twitchings and even convulsive movements have

disappeared, and there is block, would you then give a drug having a curare-like action?

Dr. Riker: No, I would not.

Visitor: Why not?

Dr. Riker: The situation is complex, and I would not increase or compound complexities. The nature of the blockade is different in each case. The blockade from anticholinesterases is the so-called depolarization blockade. The blockade produced by curare is quite the opposite. The two are mutually antagonistic, but to achieve this antagonism involves too many factors that are beyond our control. It would endanger the patient, since it is possible to give enough curare suddenly to swing from one type of block to another. In muscle, with its numerous motor units, it is likely that half may be blocked by one mechanism and the other half by another.

Dr. Reader: If an individual is poisoned by TEPP severely enough to cause serious symptoms, how soon after exposure must atropine be given?

Dr. Riker: TEPP is a good example since it reacts with cholinesterase with extreme rapidity; and if the dose is large, death may occur in a matter of 10 or 15 minutes. However, if treatment can be instituted within 10 minutes, you stand a good chance of saving the patient.

Dr. Garb: With parathion, however, the dangerous effects may be delayed considerably. It is possible for a patient to have minor symptoms which are controlled by relatively small doses of atropine and then 24 hours later to develop severe symptoms. The AMA Committee on Pesticides has therefore recommended that any patient given atropine for poisoning be watched closely 24 to 48 hours for signs of respiratory embarrassment. Once atropine has been given, the patient must be observed every few hours to make sure he does not develop respiratory difficulties.

Dr. McKeen Cattell: Are sedatives useful or contraindicated in poisoning by these compounds?

Dr. Riker: It can be shown that the addition of barbiturates to atropine therapy will help control central symp-

toms I would not hesitate to use barbiturates in those cases where there is excessive central stimulation

Dr Modell Isn t the excitement controlled almost immediately by atropine alone in many instances?

Dr Riker I think atropine will control it, but I would also use a barbiturate if necessary

Dr Reader If you use the large doses of atropine isn t there the danger that you may pass the point of a neutralizing effect on the anticholinesterase? Then the atropine itself might have a powerful excitatory effect which should be treated with barbiturates

Dr Riker The biggest dose of atropine I ever gave in man 4 mg intravenously, did not produce central excitement

Dr Modell In one patient to whom we gave about 6 or 7 mg there was excitement and some delirium I don t think doses of 4 mg are likely to cause excitement or hyperthermia

Dr Cattell Even though small amounts of atropine are usually used it is worth noting that it is one of the safest drugs we have I am not sure that anybody ever died of atropine

Dr Reader You mean the Borgias did not really use belladonna?

Dr Garb Probably not

Dr Cattell The fatal dose is probably of the order of 60 or 80 mg or about 200 times the usual clinical dose

Dr Reader You destroyed the whole myth in my mind

Dr Garb Doesn t all this apply also to the management of poisoning by the newer war gases?

Dr Riker Yes it does Of course, under war conditions supplies and personnel are not so readily at hand

Dr Garb We might say a few words about the later management of patients poisoned by the anticholinesterases Their sensitivity to these poisons may persist for many weeks after an acute episode If the patient returns to work which brings him in contact with the sprays he may again develop an acute episode on even minimal exposure They are highly sensitive to these substances The Committee on Pesticides

therefore advises that their cholinesterase level be tested before allowing them to be exposed again

Dr Modell How about people who eat apples sprayed with these poisons?

Dr Garb TEPP and HETP are hydrolyzed in a few hours and there is no appreciable danger from them Parathion persists for a much longer time and frequently is absorbed into the waxy rind of apples However, if the fruit is sprayed and harvested in accordance with the recommendations of the Department of Agriculture, there should be no real danger

Dr Reader What about arsenic?

Dr Garb Arsenic is not destroyed, it remains on the fruit

Dr Reader The lay public has a firm notion that many vegetables and fruits are covered with arsenic sprays and should be peeled before eating to prevent poisoning Is this a serious consideration?

Dr Cattell Yes, there is reason for that suspicion Arsenic and lead are frequently used in orchard sprays

Dr Reader What about nicotine used in sprays? How would you treat nicotine poisoning?

Dr Riker There is no need for atropine here, but an antidote is necessary Nicotine is a serious poison and it acts on the neuromuscular junctions, on the autonomic ganglia, and centrally The central effects should be controlled, and we should be prepared to aid respiration in peripheral paralysis The control of the central excitation is best accomplished with the barbiturates

Dr Modell Since Dr Gold is not here, I wonder if I could tell one of his stories about nicotine poisoning We ought to mention, by the way, that nicotine used as a plant spray is not nicotine but nicotine sulfate and is not absorbed through the skin

In the case described by Dr Gold, the patient sat in a pool of nicotine in a little garden house and absorbed enough through his skin to produce convulsions He was brought into the hospital The treatment consisted of removing his clothes He promptly got better, was given his overalls to

put on, and discharged. He dressed and had barely left the hospital when he was brought back in convulsions and undressed again. In treating poisons absorbed by the skin it is not enough to take off the patient's clothes; the garments have to be thoroughly washed or destroyed.

Dr. Reader: The material vaporized to kill insects has caused a considerable amount of trouble. What is the problem there?

Dr. Garb: The recommendations of the various regulatory committees are not properly followed. The vaporizers are safe only if the right degree of heat is applied, only if ventilation is adequate, and only if an approved type of insecticide is used. These appliances should not be used in living quarters, sleeping quarters, or any place where food is stored. They should not be used at all unless they include automatic devices to turn them off if heating current becomes too high and so vaporizes excessive amounts. However, these regulations are largely ignored by manufacturers, distributors, and advertisers. Fortunately, most of the insecticides in general use are not acutely toxic; however, they do produce considerable chronic toxicity.

Dr. Reader: How is this manifested?

Dr. Garb: In the few case reports I have read, it gives rise to skin rashes or vague, generalized feelings of sickness, headache, nausea, lethargy, and so on.

Dr. Reader: So that in our patients with these symptoms the possibility of a vaporizer lurking somewhere should be considered?

Dr. Garb: When a patient has obscure symptoms of this kind, it might be a good idea to ask if he uses a vaporizer at home or in the office.

Visitor: I have seen a case of allergy to a type of pesticide used for destroying wood parasites.

Dr. Cattell: How about fluoroacetate? That has become important.

Dr. Reader: How is it used?

Dr. Cattell: It is one of the most effective rat poisons, but its use has been limited by law. It may be used only by

food is stored. Suitable protective devices, such as automatic turn-off of overheated vaporizers, should be employed. The warnings about the use of these vaporizers are often ignored, and some patients with obscure generalized symptoms may be suffering from chronic toxicity produced by exposure to vaporized insecticides. The problem of residual sprays on fruits and vegetables was discussed.

Choice of Therapy in Intermittent Claudication

Dr William T Foley This afternoon our topic is the treatment of intermittent claudication Judging from the numerous drugs of all types that are offered to the profession for treatment of this condition, it is a fruitful field for discussion To open the conference we have Dr Eugene Simon, a member of the staff of the Medical Vascular Clinic, who has been doing some interesting work on this problem

Dr Eugene P Simon In opening a discussion on the therapy of intermittent claudication it seems appropriate to define the term and to outline briefly the pathology with which it is usually associated Intermittent claudication is a symptom which may present itself as cramping or aching pain or extreme fatigue in one or more of the muscle groups of the extremities It appears after walking and is relieved by rest Characteristically relief follows cessation of activity without change in weight bearing or in the position of the extremity The calf muscles are most frequently involved It always means insufficient arterial blood flow to the involved muscles While it has been demonstrated that claudication may accompany severe anemia without vascular disease, the vast majority of patients are found to have occlusive disease of the arteries in or leading to the involved extremity The major causes of such occlusive processes are arteriosclerosis obliterans thromboangiitis obliterans embolism, and thrombosis There is no agreement concerning the possibility that vasospasm in an otherwise normal arterial tree may cause claudication Exercise usually increases peripheral arterial pulsations

The physiological pathology of pain due to muscular ex

that the same treatment will increase blood flow to the muscles and relieve the pain of intermittent claudication. There is increasing evidence that measures which augment cutaneous blood flow may actually deprive deep muscular structures of blood, a finding which coincides with the occasional clinical observation that claudication may become more severe under treatment with a commonly used drug of the cutaneous vasodilator family. Post mortem studies in arteriosclerotic extremities reveal a richness of collateral circulation which apparently develops in response to tissue ischemia, and which surpasses the fondest hopes of those who use one or another of the vasodilating agents in the expectation of improving the circulation.

In treating the patient with arteriosclerotic intermittent claudication we have considered it necessary to avoid any substances which might further compromise the circulation through collateral channels, and we therefore recommend complete cessation of smoking. When intermittent claudication is accompanied by increased cutaneous vasomotor tone or skin ulceration, we feel justified in recommending one or more of the measures or drugs commonly recognized as cutaneous vasodilators. Reflex heat, the oscillating bed, warm baths, alcohol, Priscoline, Dibenzyline, and other sympatholytic agents are prescribed. Surgical sympathectomy, although it may improve skin circulation, may increase the severity of intermittent claudication. When skin abnormalities and claudication coexist, therefore, we are less likely to recommend sympathectomy.

In treating the arteriosclerotic patient who complains only of claudication and who presents a rel[illegible] normal skin cir-

claudication Without being at all dogmatic, we have gradually come to recognize that much of the benefit in cases of intermittent claudication previously attributed to vasodilator drugs or sympathectomy was probably due to the slow development of collateral circulation in response to ischemia Consequently we advise patients with claudication to walk twice a day to the point of pain and in general to keep walking as much as possible, if necessary at a slower rate, in order to avoid pain

Although it is now out of vogue, the use of various tissue extracts was at one time popular in the treatment of intermittent claudication Deproteinated pancreatic extract given intramuscularly exerting its effect through an undefined mechanism was felt by early workers to improve walking tolerance although it did not improve the circulation It is difficult to interpret most of the studies using this drug because of failure to employ adequate controls

It is apparent that no single drug or other treatment can be relied upon for relief in all cases of intermittent claudication The physician faced with this complaint must rely on those treatments which seem most appropriate for the underlying disease He must teach and advise those general measures of hygiene and prevention which have proven value in the care of ischemic extremities Such measures include the prevention or prompt care of infection or fungus infestation and the avoidance of applying heat or cold directly to the extremity The doctor may wish to try one of the cutaneous vasodilating drugs but he must be aware of the possibility that needless expense or increased symptoms may be the only result Long walks at a slow rate, and occasional walks to the point of pain but no further seem to be a rational therapeutic regime When improvement occurs as it frequently does on such conservative regimens the physician should remain a cautious observer who avoids the temptation to relate improvement to one or another particular part of the total treatment program

Dr Foley Dr Simon has made some flat statements Among other things he stated he didn t think sympathec

mittent claudication has been aggravated by sympathectomy. This evidence makes me feel quite strongly that sympathectomy should not be tried in patients unless they have a disorder of skin circulation.

Dr. Foley: Dr. Wright, a point made by Dr. Simon was that tobacco smoking is almost as important in arteriosclerosis obliterans as it is in thromboangiitis obliterans. Would you give us your view on that?

Dr. Irving S. Wright: There may be two aspects to tobacco in thromboangiitis obliterans. In addition to the vasoconstrictive effect of tobacco there seems also to be an inflammatory reaction. Whether it can be called a true hypersensitivity or allergic response is doubtful, but people who have quiescence of thromboangiitis obliterans may, within a few days after resumption of smoking, again have an acute inflammatory and later gangrenous reaction in a digit. This has happened frequently. On the other hand, in arteriosclerosis obliterans the effect of tobacco seems to be largely vasospasm of the small vessels. The small vessels and collaterals that are just beginning to open up to compensate for the ischemia produced by occlusion of major vessels can respond to vasoconstrictive influences. Therefore, the very thing that we are trying to bring about, namely, relaxation of the vasoconstriction, is counteracted by smoking. Today the leading vascular clinics in the country agree that smoking definitely retards improvement in arteriosclerosis obliterans.

I might say a few words about sympathectomy, since it seems to be a controversial subject. It may be used in some cases of thromboangiitis obliterans, but most cases can be handled satisfactorily following cessation of smoking without sympathectomy. If, after the person has stopped smoking for more than a month, the disease does not respond, the ulcers do not begin to heal, the extremities do not improve in terms of decrease of cyanosis, pain, and coldness, sympathectomy may then be considered. We have found sympathectomy to be of little value in the treatment of arteriosclerosis obliterans except for an occasional superficial ulcer. It is valueless in the treatment of intermittent claudication because it does not increase the blood flow to the muscles but

only to the skin There is absolutely no use performing this operation in either arteriosclerosis obliterans or thromboangiitis obliterans if the patient continues to smoke We have seen patients develop multiple gangrene of the extremities after sympathectomy when smoking continued We do not consider sympathectomy until the patient has shown that he can stop smoking

Dr George G Reader Is nicotine the cause of vasoconstriction? Does inhaling make any difference?

Dr Wright There is evidence that it is the nicotine which produces the vasoconstriction, since nicotine in very dilute amounts intravenously produces the same effect Furthermore, we have made up cigarettes of a great variety of substances that do not contain nicotine and had the patients smoke everything from cubebs to old leaves At one time we wondered whether the cigarette paper was important, so we made cigarettes of chopped cigarette paper It was pretty rough on the smokers because their throats became raw, but it had no effect on the vascular bed We should remember that a person need not inhale nicotine to obtain a vasoconstrictive or toxic effect One drop of nicotine 1 1000 on the gum of a dog will frequently kill it quickly Probably when nicotine is inhaled the reaction is more rapid and more complete However, it is quite potent when absorbed from the mucous membrane Therefore, failure to inhale would not protect the patient.

Dr Foley Dr Cattell, could you tell us something of the pharmacological activity of nicotine in relation to vascular disease?

Dr McKeen Cattell I can add little to what Dr. Wright has said There is a marked effect on blood pressure caused by the vasoconstrictor action It is interesting that the nicotine alkaloid is one of very few drugs that is ab[illegible] directl[illegible] by the skin We demonstrate [illegible] bing very small amount on a cat [illegible] tc [illegible] of the animal

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Dr Janet Travell Dr [illegible]

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I believe Dr Travell has some data relating to spasm in intermittent claudication

Dr Janet Travell Dr Rinzler and I found that ethyl

really crystallized. For a while I felt that anticoagulants were not indicated in a person with intermittent claudication because of the long duration of this condition. Recently, because of some clinical experiences, I am beginning to change my attitude.

Dr. Foley: Your point of view is that it might be of value, not in the treatment of intermittent claudication but as prophylaxis in the arteriosclerotic process to prevent further thrombosis, is that it?

Dr. McDevitt: Yes. Recently there has been some evidence from pathological studies in one of the New England hospitals showing that sometimes the occlusive process may extend and thus block off those points at which the collaterals branch from the main vessels.

Dr. Garb: Is it advisable to use analgesics such as alcohol and aspirin in patients with intermittent claudication? Would they increase the capacity for walking, or would they cause trouble?

Dr. Simon: We traditionally prescribe alcohol. Whether its effect is upon the circulation or the cerebrum, it seems to help many people. I think it is both sedative and analgesic, and such effects are most important.

Dr. Gold: Do you tell them to take it whether they like it or not?

Dr. Simon: Usually. We are unlikely to tell a teetotaler to take brandy 3 times a day. Analgesics like aspirin just don't seem to help the periodic pain, and certainly narcotics of the opiate family would be contraindicated in a chronic process such as this. Sometimes when a patient is told to stop smoking, it is helpful to allow him occasional drinks.

Dr. Travell: How about nitrites?

Dr. Simon: I would like to turn that question over to Dr. Foley.

Dr. Foley: Arteriosclerosis in the limbs is often associated with coronary artery disease, and we have patients with both diseases. One patient I know carries nitroglycerine with him, and when he gets an episode of angina pectoris, he takes

it. He also has intermittent claudication. His walking distance is greatly increased after nitroglycerine.

Dr. Wright: Does he stand still immediately after taking the nitroglycerine or does he keep going?

Dr. Foley. This particular chap is quite a hunter, and ordinarily he cannot keep up with his hunting mates. If, when they stop, he prepares himself by taking the nitroglycerine ahead of time, he can keep up

Dr. Gold: I note that you consider angina pectoris analogous to intermittent claudication Would you say that the precautions needed to evaluate the effects of treatment in patients with angina pectoris should be followed in evaluating the effects of treatment in intermittent claudication?

Dr. Simon Yes That is why we employed the double blind technic. Without it, it would be exceedingly difficult to evaluate the results properly

Dr. Gold What about night cramps in intermittent claudication? The phenomena are different, but how clear is the distinction between them?

Dr. Foley Night cramp is something that has always mystified me, and I have never heard a good explanation of what it is. From a physiological point of view, Dr Cattell, can you tell us what a night cramp is?

Dr. Cattell I believe it is a spasm of the skeletal muscle.

Dr. Reader Caused by inadequate circulation?

Dr. Cattell Not necessarily

Dr. Wright Perhaps it would be a good idea to have a session on night cramps There is a great variety of factors which can produce them, from having the sheets too tight to venous dilatation They are quite common in people with massive varicose veins This is a subject with many interesting angles, and I doubt if it could be developed so late in the session.

Dr. Foley Before we finish, I would like to ask Dr Wright to discuss the long range outlook in patients with intermittent claudication

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Use and Abuse of Physical Therapy

Dr. Kristian G. Hansson: The subject of the conference today is the use and abuse of physical therapy or physical medicine. I felt fairly certain that the range of our activities was well known and that the field did not require a definition, until I received a telephone call a week ago which made me change my mind. The call was from an undertaker who was troubled by the possibility of danger to himself from exposure to bodies of patients who had been treated with isotopes. He thought this exposure might hurt him; and he thought that since I was engaged in the field of physical medicine, I might be an expert on that subject. As you know, *physical medicine had its start during World War One* and was developed further in World War Two. This field consists of three broad divisions, physical therapy, occupational therapy, and rehabilitation. Physical therapy deals mainly with the use of physical means such as heat and cold, ultraviolet radiation, water, electric currents, and exercise of all kinds. Occupational therapy is exercise with a purpose. Rehabilitation deals with the matter of teaching the patient to get along as best he can with what he has. The discussion will be opened by Dr. Austlid, who is Assistant Director of Physical Medicine at the Hospital for Special Surgery.

Dr. Olav Austlid: There are two primary effects of electricity on human tissue, namely, the ionic or chemical effects, and the heating or thermal effects. Generally, the ionic effects are exerted by galvanic low frequency current, while the primary heating effect is exerted by the high frequency current. When a direct current passes between two electrodes in an electrolytic solution, we know that positive ions will

be attracted towards the negative pole and the negative ions toward the positive This same transfer or iontophoresis will occur when an electric current like the galvanic or faradic current is applied to the body If an interrupted galvanic or faradic current is applied and the negative electrode is placed over the motor part of the nerve or muscle, there will arise a stimulation of the corresponding nerve or muscle which will result in a muscle contraction This stimulation is due to H ion concentration under the negative electrode This stimulating effect of the galvanic and low frequency currents is used for testing muscles and nerves for the so-called reaction of degeneration and is also used for stimulating atrophic or paralyzed muscles On the other hand, in high frequency currents of 1,000 000 cycles or more, the duration of each single impulse is much below the effective time for ionic concentration Consequently we cannot get any stimulating effect on muscle or nerve, but if the current is applied with sufficient intensity, we will get a heating effect It is this heating effect of the high frequency current that is used for therapeutic purposes We call it medical diathermy It is used in two forms short wave and micro wave Short wave has a wave length varying from 7 to 30 meters, and we can apply it in two ways We can apply it by means of a so-called induction cable, an insulated cable which provides an electromagnetic field heating or it can be applied with condensor pads or air spaced electrodes which provide an electrostatic field heating Microwaves, as the term implies, are short wave lengths usually about 12 2 cm The radiation of microwaves has somewhat the properties of light in that they can be reflected and diffracted The energy is beamed from an antenna, and the heat can then be directed and focused It is very convenient to apply but it can heat only a small area at one time

The physiological and clinical effects of diathermy are due to the raising of the temperature in the tissues that are heated Whenever heat is applied to a part of the body from an external source, the vasomotor mechanism will respond in an effort to dissipate the excessive heat There will occur

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stimulate atropic and paralyzed muscles, especially in peripheral nerve injuries where regeneration of nerve is anticipated. If a current is used with sufficient strength to cause strong contractions, it will delay the atrophy and enhance the recovery of muscle. It will, of course, have no effect on the regeneration of the nerve itself. In stimulation of denervated muscles the most common currents used are the interrupted galvanic and the slow sinusoidal.

Dr. Hansson: Dr. Lorenze will take up the discussion from this point.

Dr. Edward J. Lorenze, III: I would like to make a few remarks of a general nature on the problems of rehabilitation and also say something about the methods that are employed. The goal of rehabilitation has been very broadly defined by the Barach committee, and it is briefly this: to achieve the maximum function and adjustment of a disabled person, and to prepare him physically, mentally, socially, and vocationally for the fullest life compatible with his abilities and disabilities. This formulation expresses a principle of medical practice which applies across the board to every medical condition and is not really limited to any particular group of conditions treated with any specific or particular type of technic. This concept has been referred to as the fourth phase of medicine. The first phase is prevention, the second diagnosis, the third specific treatment, and the fourth rehabilitation and return of the individual to society in the best possible condition. In this purpose our attention is not directed primarily to a pathological condition of a particular organ but to the state of the whole person, and the specific disease is viewed not only as a matter of concern while the patient is in the hospital, but as a condition likely to have an important bearing on the economic and social adjustment of the individual. By this concept of rehabilitation the medical profession reaffirms what physicians have long recognized, namely, that their job in connection with a chronic illness is a total medical job which begins from the time of onset of the disease or injury, or even before if one thinks in terms of prevention, and does not end until the

person is back in the community functioning in the best possible state

The technical aspects of rehabilitation relate chiefly to the restoration of function in the neuromuscular and skeletal systems The practical methods include physical therapy, occupational therapy, and retraining technics These are all very important, but of at least equal importance is the emphasis that is now being placed on the psychological and vocational aspects of the entire program The first item in care is the relief of pain It is accomplished chiefly *through the use of heat in various forms The relief is some*times only temporary, other times it is of a more permanent nature when it results in the breaking up of a cycle Even if the heat alleviates pain only temporarily, it is of considerable importance in relation to the whole problem because it permits the use of other forms of treatment that are necessary for the restoration of function For example, therapeutic exercises in one form or another, so important in the ultimate outcome, are not possible in the presence of pain Heat, which is so effective in relieving pain, plays another role in that it relieves muscle spasm which tends to persist after it is *initiated* by a *temporary* painful *condition*

A major cause of pain in muscular and skeletal disorders is abnormal body mechanics This may arise from paralysis, weakness, or contractural deformities in relation to weight-bearing positions The resulting malalignment of the body tends to give rise to painful syndromes of various types For example, flexion contractures of the knee are likely to cause pain not only in the knee and muscles surrounding the knee, but may throw out of line the mechanics of the spine and hips giving rise to pain syndromes in those areas as well In addition to exercise for the purpose of correcting or preventing *deformities and muscle imbalances* various forms of bracing are used, particularly for the lower extremities

There are several forms of therapeutic exercise The simplest one is the so-called passive exercise The muscle does not do any active work The person administering the

the patient may lack the emotional maturity or drive to carry out the necessary measures in rehabilitation although he may possess the physical ability to do so It is quite different from treating a case of pneumococcal pneumonia where generally all one has to do is apply the medicine and good results may be expected to follow In the program of re habilitation one cannot force anything upon a patient He cannot be forced to contract the muscle He must be in a frame of mind in which he wishes to do it

As I have already mentioned, the matter of rehabilitation does not end here There still remain the matters of social adaptations and vocational guidance, for one of the most important aspects is that of getting the individual back to work

Dr Hansson Are there any questions?

Dr Harry Gold In relation to the very interesting re marks of Dr Lorenze, I should like to recall a demonstration in rehabilitation which I witnessed a few years ago The patient was an old man, just skin and bones, who had for many months been completely incapacitated and confined to bed, being fed by others, and having to have his personal hygiene managed very much like a baby s He was taken in hand by an expert in rehabilitation whose main concern was with the problem of convincing the patient that he could do a great deal more than he did and that most of the things that were now being done for him he could learn to do for himself The result was truly remarkable After some weeks of this kind of training, the patient was able to get in and out of bed, sit in a chair, walk, feed himself, and look after his bowel, bladder, and bath without any help This restora tion relieved a great many hands that were previously needed to keep him alive It is of course easy enough for us to say that many of these patients can do more for themselves than they think they can, but the real job is that of getting this idea across to the patient and developing in him an interest in trying

Dr Lorenze This point of view cannot be stressed too much It is my belief that the goal of treatment that can be

attained in these cases is not that of creating a new function but of reactivating residual ability not at first apparent to the patient In this connection I sometimes wonder about the validity of the theories of neuromuscular re education technics which involve the idea of rechanneling motor impulses through new pathways

Dr Gold Perhaps we can carry the point a bit further by asking this question What does it mean if such an elderly patient as I have just described states I cannot lift my leg at the hip I just can t do it and that s all there is to it Yet when the expert in rehabilitation is finished with him he can do it

Dr Lorenze The ability to do it was there all the time I imagine that the individual who goes to bed one night and wakes up the next morning with a paralyzed right side suffers not only the organic injury but a psychological injury When you examine such a person in bed you discover that he is unable to move the leg at all Then if you stand him up with a person on each side for support you may become aware of the fact that there is some flexion at the hip perhaps also some contraction in the hamstrings The paralysis in this person was not really complete but he thought he was completely paralyzed and for psychological reasons he failed to initiate a movement The capacity for movement was there all the time This is the thing that can be further and further developed and it is a thing that happens in the program of rehabilitation training We frequently see patients in bed who seem to be completely paralyzed who shortly after we begin to work with them begin to show muscular action of varying degrees proving that the paralysis is not complete In terms of an active life the disability of the hemiplegic seems like a catastrophe with nothing hopeful in it However those people who have suffered a hemiplegia and have already passed through a period of complete helplessness are often able to derive a great deal of comfort out of the small improvements in their capacity to take care of themselves

Dr George G Reader Dr Hansson we have heard a good

Dr Reader Is there any advantage in one source of heat over another, let us say, diathermy as contrasted with infra red lamps?

Dr Austlid Theoretically there is quite a difference but in practice there is not so much A short wave with an induction cable, as I mentioned, provides electromagnetic heating By this method the muscles and the vascular bed get most of the heating On the other hand, with condenser pads you get most of the heating in nonconducting tissue like skin, fat and bone However, because heat is dissipated through the circulating blood and temperature is also lowered through conduction, much of the difference between these forms of therapy disappears Infrared gives a much more superficial heat It is preferable, for instance, for application to the hip in arthroplasty with a vitallium cup Here it is undesirable to heat the deeper structures for reasons I stated earlier in the conference Still, by heating the skin and superficial tissues you can increase the circulation in the part to which it is applied

I would like to mention one point in regard to the misuse of the technics of physical medicine Patients are often referred to us from other clinics without a diagnosis and presumably because they do not know what to do with them Physical therapy becomes a wastebasket for undiagnosed cases Many of these are in pain, and they are referred with the suggestion that we use some form of heat If there is no tenderness and no spasm, heat is not likely to accomplish very much We should avoid treating these patients unless we know as much as we can about what they have

Dr Seymour H Rinzler Could we have a word about the kind of machine one should have in the office high or low frequency?

Dr Hansson The Federal Communications Commission has something to say about that

Dr Austlid For short wave machines there are 3 different frequencies The wave lengths are approximately 7 5, 10, and 20 meters In the microwave, several frequencies are allowed but the one most commonly used is 12 2 cm

Dr Hansson I would suggest that when you secure an apparatus you look for the tag "Accepted by the FCC'

Dr Rinzler Which ones do they not accept?

Dr Hansson The long wave machines are no longer acceptable According to law they had to be discontinued by July of 1953

Dr Gold In the way in which doctors by and large use these machines and considering the conditions for which they are usually employed would you not agree that their effect is simply that of a placebo in about 90 per cent of the cases?

Dr Hansson I would say yes

Dr Austlid In orthopedic hospitals and in hospitals having a good physical medicine department, one is apt to encounter a good deal of rationality in the application of physical therapy Much is now known about the conditions in which particular technics are most useful, and this knowledge is frequently applied One must still guard against a practice which continues because of the fact that most physicians are not sufficiently familiar with specific indications for particular physiotherapies It is not uncommon to have the doctor order some diathermy for a frozen shoulder It has little effect on the frozen shoulder, but what actually would have an effect is often omitted namely, regular exercises after the heat, the heat serving to loosen up the joint and the active exercises tending to prevent stiffness The heat itself will do very little

Dr Frank C Ferguson, Jr I have often been puzzled by the apparent limitations in the benefits of physiotherapy A patient with bursitis might receive diathermy in a course of 8 or 10 treatments over a period of about 3 weeks with some improvement, and then for some reason the benefits cease as if the patient had developed a tolerance to the treatment

Dr Lorenze This may be due to the use of a single modality in treatment with physical measures It is a mistake to use one method to the exclusion of others I know of no condition which is properly treated by diathermy alone, by

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Management of Hematemesis Associated with Portal Hypertension

Dr Thomas P Almy The subject of this afternoon's conference is hematemesis, a manifestation of disease which is rightly regarded by the patient and the physician as an extreme emergency. A great amount of experience in the management of this complication has been had by the surgical service of this hospital, and we shall lean heavily upon their experience at this conference I think it well to define the area of the discussion rather sharply because obviously hematemesis has many causes, and we could say a little about many things and come out with nothing very useful As you know, it is commonly a manifestation of peptic ulcer, but inasmuch as peptic ulcer has been extensively discussed in both its medical and surgical aspects in other conferences of this series, we shall not consider it at this time * The relationship of portal hypertension to hematemesis is clear and is one in which our speaker has had special experience, therefore, we shall beam the conference in that direction The chief speaker is to be Dr Charles Gardner Child of the Department of Surgery

Dr Charles G Child Massive bleeding from esophageal varices developing secondary to portal hypertension is a medical and surgical catastrophe the importance of which has only been recognized in the relatively recent past When I say "relatively recent," I mean that as a clinical entity this source of massive upper gastrointestinal bleeding has

* Conf 5 Management of Peptic Ulcer with Protein Hydrolysates *Cornell Conferences on Therapy*, Vol III 1948 Conf 14 The Medical Treatment of Peptic Ulcer *ibid* Vol VI 1953

only been accorded serious attention within the past 20 years, and its treatment has only been developed within the last 5 to 8 years Although esophageal varices have been recognized by pathologists for well over a hundred years, their clinical significance, their relationship to cirrhosis and to portal thrombosis and their association with portal hypertension is, as I have said, really a new development As a matter of fact an American physician, one Dr Powers, was probably the first to discover an ulcer penetrating an esophageal varix in a Negro who had died shortly after an exsanguinating esophageal hemorrhage Another concomitant of cirrhosis, massive ascites, had, of course been known for many years, and its treatment by paracentesis goes back to ancient times Interestingly enough, however, though cirrhosis varices, and ascites were recognized many years ago as distinctive entities, they were not related to portal hypertension until about 1930 At this time McIndoe in this country and MacMichael in Scotland fell upon the idea that portal pressure was probably elevated in patients with esophageal varices

Dr Louis Rousselot, working under Dr Whipple in the spleen clinic at Presbyterian Hospital must probably receive credit for first demonstrating that in patients with cirrhosis, splenomegaly, and varices, as well as in patients with so-called Banti s disease, the portal pressure is in truth elevated many times above normal You all will recall, I am sure, Eck's famous fistula, and I think that today many believe that Eck advised his famous operation for diminishing abnormally high portal pressure I do not believe this to be the case true it is that Eck advised the use of his fistula in patients with cirrhosis, but his objective was to decrease the formation of ascitic fluid, not to lower portal pressure in patients with esophageal varices

With Dr Rousselot's demonstration of portal hypertension in 1937 or so, progress in applying the Eck fistula to patients with bleeding esophagogastric varices has been rapid Preoperative and postoperative care, particularly in the patient with liver disease, has been improved technics in vascular surgery have been perfected and diagnostic

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the vena cava. The portal vein at the porta hepatis is ligated and the cut end implanted into the wall of the vena cava. By this method, degrees of pressure in the portal bed, say of 36 to perhaps 45 cm. of saline, may be lowered to safe levels of 18 to 22 or so, a very appreciable drop in pressure.

The second type of shunt that is employed is one in which the spleen is removed and the splenic vein implanted into the renal vein, again usually in the end-to-end position. Again drops in pressure from 36 to 45 cm. down to 18 to 22 cm. may be accomplished. Incidentally, for those of you who are not familiar with it, I might point out that the normal portal pressure is somewhere between 8 and 12 cm. of saline. Thus, though we don't drop portal hypertension entirely to normal, we come pretty close to it.

Under what circumstances are portal decompressive operations indicated? In the patient with extrahepatic block, that is, where a thrombosis has developed somewhere in the portal vein, the operation for portal decompression is invariably indicated. We know from observing many such individuals that, after they have had one hemorrhage, it is only a matter of time before they will have another, and, if allowed to go on long enough, they will usually succumb in one of these hemorrhagic episodes. Furthermore, one can hardly conceive of a more psychically traumatic situation than a young individual running around always wondering when he is going to have another massive esophageal hemorrhage. These people are good operative risks primarily because their liver function is normal. The development of a block in the portal vein does not lead to hepatic damage. The type of operation in extrahepatic block must almost invariably be the spleno-renal shunt. The portal vein, due to its obliteration, is unsuitable for any form of vascular anastomosis. The spleno-renal shunt is then the type of operation which is useful in young patients with extrahepatic block.

The majority of patients in the older age group who present themselves with massive esophagogastric hemorrhage from varices will be found to be suffering from cirrhosis of

the liver. There are many forms of cirrhosis, and patients with cirrhosis present themselves in all stages of their disease. Only a few, however, are suitable for portal decompression. In the first place, they must develop portal hypertension. We don't actually know how many patients with cirrhosis do not develop portal hypertension, but the number must be rather large. We have no accurate figures, because after death the measurements of portal pressure are not accurate. The individual with cirrhosis and ascites is not considered suitable for operation, for there is no evidence to lead us to believe that the shunt in any way improves liver function, and, by bitter experience, we have learned that there is very little hope that we can control ascites by a shunt. The patient who comes up for serious consideration is the one with cirrhosis who has varices and who has had one or more hemorrhages but no ascites These are the ideal group for portal decompression The fact that they have never developed ascites is a crude measure of the fact that their liver is pretty well compensated. Fatal hemorrhage constitutes an ever-present threat to life unless these patients are treated by portal decompression.

Another group consists of individuals with varices who have had a hemorrhage and who have or have had ascites. I have separated into a separate group those in whom the ascites can be controlled. A number of these, for instance, develop ascites rather suddenly, often secondary to the depletion occasioned by a hemorrhage. If such patients can be brought into a proper state of nutritional balance, the ascites may disappear. Such individuals then, we believe, become suitable for operation.

Next we come to that group of patients who have ascites, marked wasting, perhaps a history of coma, varices, and have had one or more hemorrhages. Their liver function is so poor that, even with our best efforts, we are unable to control their accumulations of fluid. In this group, portal decompression is probably contraindicated. The chances are about even between death from hemorrhage or primary liver disease. Because of their poor liver reserve, it is in this group

Dr Almy Dr O Sullivan do you have any views on that?

Dr Ward D O'Sullivan That has been tried by some of the workers in the Mayo Clinic However, I think it has been superseded by direct and indirect portocaval shunt. It is not an easy procedure, and I believe most injections are not in the vein proper, but around it in the attempt to produce some sort of scarring It is difficult to work in a few centimeters of narrow tubing

Dr Michael Lake What about actual resection of a portion of the esophagus with varices when the shunt is not practical for anatomical reasons? I know of one case where that was done

Dr Child That is a much discussed form of therapy at the present time Dr Wangensteen originally proposed that the basic defect in esophageal varices is of course, the varices and that bleeding occurs because of peptic erosion into a large lake of blood under high pressure He has concluded that the most logical treatment is resection That has been done in a number of clinics, but I think the consensus today is that decompression is the preferable operation There are times when decompression either fails or is not applicable For instance in extrahepatic block the portal vein is useless If spleno renal shunt has been attempted and is unsuccessful, that source is no longer available Such individuals are now operated upon, with the idea that if a suitable lake or a large dilated area can be found, perhaps at the junction of the splenic and portal vein, anastomosis should be tried, using a free vein graft, if necessary

When all of those avenues are closed and the patient continues to have hemorrhagic episodes we are reduced to some form of esophagogastrectomy

Dr Lichtman Perhaps there is danger that anyone reading this conference will gain the impression that all there is to the management of hematemesis in liver disease is surgery

I think there should be some discussion on preparing the patient for operation Presumably Dr Child would resort to surgery only after he is fully convinced that the patient is a good risk Suppose the patient is bleeding

copiously, the stools tarry, hemoglobin dropping, and the patient is going into shock. I don't think we can treat bleeding from portal hypertension in the same way we treat arterial bleeding in an ulcerated area in the duodenum. I consider the bleeding from a varix less of an emergency than a bleeding peptic ulcer. It requires courage to hold back transfusion. If the patient should die, one would fear that he had been undertreated. Yet, on the other side of the ledger are the large series of cases from the Goldwater Memorial Hospital in which, despite numerous transfusions, the patient died. It is my opinion that little is accomplished by transfusion if the patient continues to bleed. I prefer to watch the circulation and the hemoglobin, see that the patient is comfortable, and withhold narcotics. Most patients will survive the bleeding episode, and from there on an opportunity is afforded to do the tests upon which one decides whether or not to resort to surgery. To control hemorrhage, a balloon may be passed. However, this is fraught with difficulties, and I am sure anyone who has resorted to this procedure will not be very enthusiastic about it. In the first place, the patient must be sedated to a marked degree, and this is undesirable in a patient with liver disease. The deep sedation may result in coma, and that is an unfortunate occurrence with hemorrhage which may necessitate the removal of the balloon. In that case, there is danger of aspiration pneumonia. Further, the patient cannot eat while the balloon is in place so that intravenous therapy may be required. For these reasons the balloon procedure is not recommended for the usual case of bleeding in which the hemoglobin has not dropped considerably. I have treated such patients conservatively for years with excellent results. The patient who dies with the first hemorrhage has an extreme degree of portal hypertension, and I believe any therapy would be of little avail.

Dr. Almy: Dr. Lichtman, you made an important point about transfusion. What are the indications for transfusion?

Dr. Lichtman: I don't think it would be hazardous to give an initial transfusion of a liter of blood. Sometimes I give

ing, it is extremely difficult to decide whether or not they should be operated upon

Visitor I would like to ask Dr Child about the mortality rate for this operation and how serious is it considered to be

Dr Child The mortality in uncomplicated extrahepatic block is now quite low. Over the country it is 3 to 5 per cent and provides no reason for withholding operation In series including many patients with liver failure or borderline decompensation, the mortality may be as high as 30 to 50 per cent

Visitor How long should the balloon be left in place after the bleeding has presumably stopped, and how do you start the patient on oral feedings?

Dr Child The objective is to get the balloon out as soon as possible If the patient has stopped bleeding and the balloon has been deflated with no evidence of recurrent bleeding, it is removed within 12 to 36 hours

Visitor The question is, how long is it necessary to leave it deflated before removing it?

Dr Child Usually 6 to 12 hours The balloon is deflated, and if there is no bleeding for a day, it is removed, and feed ing of a soft diet would be started soon thereafter

Visitor The same day?

Dr Child The next day

SUMMARY

Dr McKeen Cattell The subject of the conference today commands our attention because it involves a condition which has defied all treatment in the past, quite uniformly fatal, and one for which a form of treatment has been de veloped in the past few years which offers much promise The patient subject to hematemesis from esophagogastric varices has hanging over his head the imminence of a fatal hemorrhage In the more conservative approach, close watch, restraint in the use of narcotics, and whole blood trans fusions are the chief measures until the bleeding comes to an end spontaneously In the more severe and persistent cases,

a balloon is inserted to the site, and the bleeding is con trolled by inflation Details of the technic and dangers of the balloon method have been given The prevention of re currences is the more important aspect of the advance in therapy It involves lowering the portal pressure by porto caval or spleno renal anastomosis This operation has proved safe and highly successful in extrahepatic portal hypertension less so and more risky in cases of hepatic cirrhosis with or without ascites There has been much interesting discussion of the proper selection of cases and experience in the procedures that help to establish the diagnosis

thetist as to whether the patient could *tolerate* anesthesia was an important factor in our decisions Patients have been accorded the usual medical therapy until considered to be in the best possible condition for the operation Finally, prior to operation, a conference is held on most patients by our interdepartmental cardiovascular group, made up of representatives of medicine, pediatrics, surgery, and the cardiophysiological group, in conjunction with the anesthetist and the surgeons

As far as the operation is concerned, the surgery of mitral disease is dependent upon the anesthesia In this group of patients, particularly those with a very low cardiac reserve, a malfunctioning heart is a common finding, as is a poorly functioning pulmonary system as the result of hypertension and sclerosis A thorough understanding of these physiological changes on the part of the anesthetist is essential, and expert administration of the anesthetic agent to maintain a high oxygen concentration in the blood is of the greatest importance Outpatients have had the benefit of meticulous induction and maintenance of a light anesthesia by our Chief of Anesthesiology, Dr. Joseph F Artusio

When preparing the patient for operation, provision is made for rapid and adequate blood replacement by suitable methods Several liters of blood are kept at hand during the operation, to be given rapidly under pressure should the washing out of intra auricular thrombi or inadvertent injury cause a loss of blood As the operation proceeds, any blood loss is carefully estimated by weighing all sponges and by measuring any blood removed by suction

After induction of anesthesia, with the patient in position, the left thorax is slightly elevated on a folded sheet placed under it from the shoulder to the level of the 12th rib The heart is approached through a left anterior, lateral incision The heart is inspected, and then while the anesthetist makes pressure upon the carotid vessels, we palpate the left auricular appendage to determine whether there are clots present, exercising care not to dislodge clots if they happen to be present Thereafter, we place two purse string sutures around the

base of it and a clamp just at the distal portion, and then we excise the tip of it. If we think there are clots in the auricular appendage we insert our finger carefully as we try to break these clots up and allow them to be washed out, losing probably 50 to 75 cc. by each manipulation Once inside the auricle, we are interested in evaluating the stenosed valve. No two valves are alike. The first thing we are interested in is the question, is there or isn't there regurgitation. If there is much regurgitation, our hearts sink a little, we know that our prognosis is not as good as when we have a pure mitral stenosis A small amount is perfectly all right Then, you palpate the valve You determine first the size of the orifice and then the mobility of the component leaves and then you seek for calcium Having gotten that information, you then proceed to enlarge this orifice which, in the majority of our patients, is less than 1 5 square centimeters in area This is accomplished by simply introducing the finger into the orifice and fracturing the valve Occasionally the valve's diameter cannot be increased by finger fracture alone, and so a valvulotome of the Bailey or Harken type is used to increase the area of the orifice at the line of the presumed commissure. It is our objective to increase this orifice from we will say, 1.5 square centimeters to 4 to 6 Generally speaking, in pure mitral stenosis we do not end up with any insufficiency. If you have a small degree of insufficiency, it may be corrected by overcoming the stenosis, if you have very much insufficiency, your chances of decreasing it are scant indeed We have operated on patients who we knew had some mitral insufficiency We have not always estimated correctly in some of these patients we found more stenosis than we had anticipated, in others we found more insufficiency than we anticipated Following the necessary enlargement of the orifice, the finger is withdrawn, and the auricular appendage is occluded by tightening up the pursestring sutures at the base of the appendage and over sewing the tip If we occlude by pressure or distortion the coronary vessels near the base of the appendage, cardiac arrest may occur We had two such patients whom we were able to resuscitate successfully without resid-

surgery that patients do die quite unexpectedly because of their mitral stenosis. I will take one minute to tell you of a patient we had about a year ago, a young Negro girl. I believe her age was in the neighborhood of 27. She was brought into the hospital for study. She was carefully evaluated, and her mitral valve was calculated by Dr. Lukas as being 0.9 square centimeter in area. She was considered in our conference on Wednesday. There was some discussion as to whether or not she had been given an adequate amount of digitalis. And so we decided to postpone our operation until the following week. At that time she had bathroom privileges, but she spent most of her time in bed. On the Sunday morning, the patient became nauseated, and we thought she had received too much digitalis. She was told to stay in bed. To make a long story short, she went into pulmonary edema and died within eight hours. At post mortem examination, the measurement of the valve orifice was exactly what Dr. Lukas had forecast. I am convinced that if we had only operated on that patient before this episode, she would have survived, and would have been a good result, because she had a valve that could be split, one without calcification, and I think a very good myocardium.

Visitor: Was that death due to pulmonary edema?

Dr Glenn: Yes.

Dr. Reader: Thank you, Dr. Glenn. That is a most remarkable record. Are there questions?

Visitor: What do you assume to be the reason for failure of improvement in the remaining 30 per cent of the cases? Do you assume that the operation failed to enlarge the valve?

Dr. Glenn: About 50 per cent of patients are improved enough to have the Heart Association classification changed one category; another 20 per cent are improved but not that much. Perhaps it would be well for me to say a word about that 30 per cent of failures. Many of these patients did improve, but they were still disabled. The follow-up has not been long enough. I don't know how the matter will stand when a more critical evaluation is carried out in about two years after the operation. It may show that patients with in-

sufficiency have also benefited. As to the failures in the patients with stenosis, there were some in whom we had not opened the valve sufficiently. That group might be considered for reoperation. There are those individuals with associated lesions that were more severe than we were inclined to believe prior to the operation. I don't think much can be done about that group. Also, there are those patients who have been disabled for a very long time and in whom too much irreversible damage of the myocardium has taken place. All of these together add up to about 30 per cent of the cases we have operated upon who have not really been helped.

Visitor: What are the subjective and objective criteria for improvement?

Dr. Glenn: The most important criterion is the patient's increased capacity for work. This has to be carefully evaluated, for patients are anxious to cooperate, and what they say about increased activity may prove misleading. However, the improvement is frequently so spectacular and early that there is no mistaking it. As we have watched these patients in the cardiac clinic over a period of time, now over three years, many of them have continued to improve. Once the improvement begins it seems to continue. We have had very few patients in whom regression occurred after a brief period of improvement. Aside from this gross evidence of improvement in terms of the patient's capacity for activity, there are the various cardiac measurements which provide supportive information, proof of the increased size of the valve orifice and diminished pulmonary hypertension.

Dr. Reader: Dr. Glenn, your remark about the information we obtain from patients sometimes proving misleading in an evaluation of the effects of the operation was brought forcibly to our attention by one of your patients whom we had the privilege of following for a period before and after the mitral surgery. It struck us that there is a psychological factor in this matter of performance. This was a young woman who had been handicapped in all her activities until the age of 35 or 40. After her valvular lesion was corrected, she was faced with a new difficulty, that of realizing that she could

Dr Glenn What do you think about that Dr O Sullivan?

Dr Ward D O'Sullivan I don t know I have often wondered about operating on people at an early age Mitral insufficiency is less apt to be present, and the immediate operative result is apt to be better The operation is more easily done, and a better job is done on young persons Yet it may turn out that in spite of the operation the disease will follow its natural course I certainly agree with the position that the operation should be performed on any person with mitral stenosis who has developed disability at an early age, and who is at the stage where he finds it necessary to curtail his activities or is advised to do so by the doctor

Dr Gold I take it that you would prefer to postpone operation until there is clear evidence that the patient is disabled

Dr O'Sullivan Yes, not just a person who has a murmur

Dr Reader Would you think a marked reduction in the size of the mitral orifice sufficient to justify the operation even if the patient is not physically disabled?

Dr Glenn Actually, at the present time we do the measurement of the orifice only in those patients about whom we are not certain and are trying to make up our minds These are usually poor risk patients The clinical picture of incapacitation is very closely related to the size of the mitral orifice In reference to your question it should also be pointed out that there is more involved than just the valve leaf I don t know this to be a fact, but I should think that there is a likelihood that some patients who are operated upon young in life and with very good results may have recurring episodes of rheumatic fever This may lead to further deterioration of the valve and more trouble

Dr Roy C Swan Dr Glenn referred to a few patients who showed some improvement for a few months following the operation which seemed not to last What appears to be the reason for that kind of result?

Dr Glenn Unfortunately only a small number of our patients have had cardiocatheterization after the operation There were two with this temporary improvement We were

chagrined to discover how small the valve orifice turned out to be. I have an idea that the apparent improvement in these two patients was due to a combination of psychological factors and the benefits of rest and hospitalization. These patients are nursed and buoyed up for a period of 10 days to 2 weeks before operation. They receive optimum care, and abundant attention is paid to all their needs. Then comes the operation, hospitalization for 2 or 3 weeks, after which they are sent to a convalescent home for such a period as they elect to stay. Naturally such an individual is going to be able to put up a better front for a period of time. We have to take these factors into consideration in judging the value of enlargement of the mitral valve per se.

Dr. Reader: I take it that what you are saying is that such a period of rest and care without the operation might have resulted in similar improvement for a while. It might be well to try this in some cases.

Dr. Gold: I would like to ask Dr. Glenn whether the various measurements, including the results of catheterization, made prior to operation, ever supply you with material which decides the question of operation.

Dr. Glenn: Would you like to answer that, Dr. O'Sullivan?

Dr. O'Sullivan: We performed a catheterization in every one of the first hundred cases. Some of these presented only a short history of symptoms. Fairly marked elevation of pulmonary arterial pressure was found by catheterization. We felt it proper to prognosticate that the pressure was going to continue to increase and that these would become very sick persons in the future. Here were, then, ideal candidates for the operation, namely, early symptomatology but with the suitable mechanical set-up for progression and permanent disability.

Dr. Gold: May I then ask you this: Could you not have obtained in another way information that has similar significance? Would you not learn the same things about these patients if on fluoroscopic examination you found marked straightening of the left border of the heart, an enlarged left auricle, distention of the pulmonary vessels? These are q

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In our small series we lost 3 patients. We could do nothing for any of these at operation. In one there was a very heavy deposit of calcium, in another there was marked mitral insufficiency with the valve being larger than the normal valve in an adult, and the third had advanced aortic stenosis.

We had all our patients come back about 2 weeks ago for review. What we found leads us to the conclusion that the operation was exceedingly worth while in that group of tight mitral stenosis without excessive calcification, without insufficiency, and without other organic lesions. Of the patients that come to our attention at the present time, we are now much more selective and tend to turn down many more than we accept for operation. Our mortality rate in this plan of practice will approach about 2 or 3 per cent.

Dr. Gold: I would like to ask whether in these groups of patients of Dr. Glenn and Dr. Lord there have been any who prior to operation were in need of intensive congestive failure therapy with salt restriction, digitalis, and diuretic agents, but in whom after operation the circulation was sufficiently restored so that this form of treatment was no longer necessary?

Dr. Glenn: Yes, we have had some of those.

Dr. Gold: Is that an exception?

Dr. Glenn: I can't give you any figures on that point, those will be forthcoming later. I can think of individual examples. The majority of these patients have to be given supportive therapy which is gradually reduced after operation and in one instance required a period of over 2 years.

In the selection of patients for the operation, it might be well to mention that this operation is very useful in pregnant women in whom mitral stenosis has created difficulties in previous pregnancies. We have now operated on 9 patients during pregnancy. On the whole, they have done very well. I believe we have had one miscarriage.

answer to this question We have one patient, the first patient we lost early in our series, in whom we suspected that the death in cardiac failure was the result of acute rheumatic fever because of the fever and the rapid pulse rate I now have some doubt as to whether the operation has any effect

Dr Lukas I am inclined to think that at operation we simply discover the active rheumatic process which may have escaped detection previously because of the absence of the usual criteria for active rheumatic fever

Dr O'Sullivan We make it a practice not to operate on anyone with clinically active rheumatic fever However, the biopsy findings at operation often come up as a surprise, for they sometimes turn up as positive when there is no clinical support for it

Dr Lukas It looks from the experience of others (the Boston series and the review of some 450 cases by Dr Ellis) that about 40 per cent of the patients are going to show biopsy findings positive for rheumatic activity regardless of what the criteria are for the selection of cases The rheumatologists generally feel that if there is clinical activity operation should be withheld, but there are contrary opinions to the effect that the young patient with a tight mitral stenosis should receive the benefit of the operation even if there is active rheumatic carditis this being kept in check with suppressive therapy before and after

Dr Reader Dr Lord I wonder if we could hear about your experience with this operation and your opinions on some of the points we have been discussing

Dr Jere W Lord, Jr My series is a small one, only 38 patients but we have gotten some fairly definite impressions from our experience with them We have come to feel in line with what Dr Gold mentioned that the clinical examination is probably the most important factor in the selection of patients The audiovisual study of the murmur as developed by Dr Butterworth has proved to be a very useful aid Dr Lukas you may recall the patient R H, whom you restudied for us You may recall that your findings were suggestive of mitral stenosis We reoperated upon her later, but found in

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nosis Mitral valvulotomy has become an accepted surgical procedure with a high incidence of successful results and the mortality reduced to a rate well within that for other operations of similar magnitude The discussion revolved chiefly around the experience with 130 cases at the New York Hospital The proper selection of cases is of paramount importance, not only from the standpoint of reducing surgical mortality, but more significantly from the standpoint of increasing the proportion of cases in which the operation proves successful against the hemodynamic disturbances of mitral stenosis Satisfactory therapeutic results in about 70 per cent of the cases and an operative mortality rate of less than 3 per cent characterize the results of the group that was discussed The extent of the improvement in the patients capacity was sufficient to call for functional reclassification (American Heart Association) in slightly less than 50 per cent 90 patients, followed for 3 months or longer

The object of the operation is to increase the size of the mitral orifice At the present time it seems that the chief beneficiaries of this operation are patients with mitral stenosis in whom there is evidence of progressive disability due to mechanical obstruction at the mitral valve The operation is successful in patients with auricular fibrillation as well as those with regular sinus rhythm and is often helpful in those who have in addition to the mitral stenosis a mild degree of mitral regurgitation It is the present consensus that bacterial endocarditis active rheumatic fever, and severe mitral regurgitation are contraindications to the operation There are some who still depend to a considerable extent on the results of cardiac catheterization for a decision on the question of selection of a patient for operation although there is in evidence a tendency on the part of others to place the greatest reliance on the clinical manifestations of mitral stenosis with a marked degree of obstruction at the mitral valve in terms of the kind of murmur on fluoroscopic examination of the straightened left border distended pulmonary vessels enlarged left auricle and history of symptoms suggesting pulmonary overfilling or pulmonary edema Much emphasis was

placed on the importance of the anesthesia in the success of the operation very light anesthesia combined with high oxygen intake and administered by an anesthetist trained in this special surgical field There was provocative discussion concerning the relative importance of physical and psychological factors in the judgment of success or failure of the operation These factors may work both ways on the one hand pointing to a restoration of the patient's functional capacity when it was only a matter of encouragement to the patient to use what capacity he had been previously ignoring on the other hand pointing to a failure of the operation by reason of psychic restraints to additional activity in one in whom the physical capacity of the circulation has been greatly improved by the operation

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